7.1.2.2 Toxicological Studies

Toxicological studies provided some evidence that $PM_{2.5}$ may impair the insulin signaling pathway leading to effects on glucose and insulin homeostasis (Table 7-4). Haberzettl et al. (2016) reported that insulin increased ($p < 0.05$) Akt phosphorylation, which is a marker of insulin sensitivity, in the aortas of mice breathing filtered air, whereas no insulin-stimulated phosphorylation of Akt was identified in short-term $PM_{2.5}$ CAPs exposed mice. This effect was also observed following long-term exposure to $PM_{2.5}$ (Section 7.2) and may precede changes in glucose tolerance or insulin resistance. When Haberzettl et al. (2016) treated mice with the insulin sensitizers metformin or rosiglitazone, aortic insulin signaling (also measured via Akt phosphorylation) was unaffected in exposed mice, whereas vascular insulin resistance and inflammation induced by $PM_{2.5}$ CAPs exposure were prevented (Section 7.1.3). Notably, treatment with or without the insulin sensitizers had no effect on blood glucose, plasma insulin levels, or the HOMA-IR or HOMA-β scores (Haberzettl et al., 2016). Liu et al. (2014b) reported insulin resistance (measured by HOMA-IR) at 1 and 3 weeks after $PM_{2.5}$ CAPs exposure. Balasubramanian et al. (2013) reported an acute increase ($p < 0.05$) in norepinephrine (NE) in the paraventricular nucleus and corticotrophin releasing hormone (CRH) in the median eminence of the hypothalamus of Lean Brown Norway rats 1 day, but not 3 days after $PM_{2.5}$ exposure. Norepinephrine increases suggest activation of the sympathetic nervous system, whereas increased CRH may activate the HPA stress axis leading to glucocorticoid release and mobilization of glucose, lipids, and amino acids to the blood stream (see CHAPTER 8).

Table 7-4 Study specific details from animal toxicology studies of metabolic homeostasis.

Study	Study Population	Exposure Details	Endpoints Examined
Balasubramanian et al. (2013)	Rat, male, adult Brown Norway or 4 or 8 mo. old JCR-LA (spontaneous obesity, hyperlipidemic, insulin resistant), n = 16	Grand Rapids, MI CAPs 519 μg/m^3 for 1 day and 595 μg/m^3 for 3 days; JCR/LA rats, Detroit, MI CAPs 291 μg/m^3 for 4 days; whole body inhalation.	Neurotransmitters (norepinephrine, corticotrophin releasing hormone, dopamine, and 5-hydroxy-indole acetic acid) levels in the paraventricular nucleus and median eminence of hypothalamus

Table 7-4 (Continued): Study specific details from animal toxicology studies of metabolic homeostasis.

Study	Study Population	Exposure Details	Endpoints Examined
Haberzettl et al. (2016)	Mouse, male, C57BL/6J, ND or HFD, 8–12 weeks, n = 4–8	Louisville, KY CAPs $PM_{2.5}$; 30–100 μg/m^3 Group 1: exposed for 6 h/day for 9 days. Group 2: treated with daily dose of water, metformin (50 mg/kg dose 2 days before, 100 mg/kg dose 1 day before and 300 mg/kg at the time of $PM_{2.5}$ exposure), or 1 mg/kg rosiglitazone 2 mg/kg 2 days before 9 days CAP exposure in drinking water.	Body weight, fasting blood glucose and insulin, HOMA-IR, organ weights, blood lipids, liver clinical chemistry, insulin signaling pathway, circulating bone marrow derived stem cells, Blood triglycerides, HDL, LDL, HDL/LDL
Ito et al. (2008)	Adult male Wistar Kyoto rats	Yokahama City, Japan CAPs collected during May 2004 (1.3 mg/m^3 ± 0.1), November 2004 (1.0 mg/m^3 ± 0.3), and September 2005 (1.9 mg/m^3 ± 0.4). Rats were exposed 4 days (4.5 h/day) or to FA for 3 days and CAPs for 1 day or to FA for 4 days	Blood pressure, HR and mRNA markers from heart tissue of HO-1, TBARS, ETA, cardiovascular disease (ET-1, ETA, ACE, ANP, BNP, Tnfα, Il-1B)
Seagrave et al. (2008)	Adult male Sprague-Dawley rats, 8–10 weeks old	Nose-only inhalation, $PM_{2.5}$ road dust from New York City, Los Angeles, and Atlanta at low (306 μg/m^3) and high (954 μg/m^3), one 6 h exposure	Heart tissue, oxidative stress, TBARS
Sun et al. (2013)	Rat, male, Sprague Dawley, ND or high fructose, 8 weeks, n = 7–8	Dearborn, MI CAPs $PM_{2.5}$; 356 μg/m^3; 8 h/day, 5 day/week for 9 days over 2 weeks, whole body inhalation	Body weight, inflammation, adipose tissue gene expression, iNOS, mitochondrial area
Wagner et al. (2014a)	Rat, male, Sprague Dawley, ND or high fructose, n = 7–8 per group	Dearborn, MI CAPs $PM_{2.5}$; 356 ± 87 μg/m^3, 441 ± 65 μg/m^3 for O_3 and $PM_{2.5}$ or O_3 alone. O_3 average was 0.485 ± 0.042 ppm for 8 h/day for 9 consecutive weekdays (Week 1 M-F, Week 2 M-Th)	Heart rate, heart rate variability, blood pressure
Wagner et al. (2014b)	Rat, male, SH (spontaneously hypertensive), 12–13 weeks, n = 8	Dearborn, MI CAPs $PM_{2.5}$; Study 1: 415 ± 99 μg/m^3 $PM_{2.5}$ Study 2: 642 ± 294 μg/m^3 $PM_{2.5}$ Study 3: 767 ± 256 μg/m^3 $PM_{2.5}$ Study 4: 364 ± 58 μg/m^3 $PM_{2.5}$ 8 h exposure repeated for 4 consecutive days	Distribution of major components, heart rate, lnSDNN, lnRMSSD, MAP, systolic, diastolic, associations between components and cardiac responses
Xu et al. (2013)	Mouse, male, C57BL//6, n = 6/group, 4 weeks old	Columbus, OH CAPs $PM_{2.5}$; (143.8 μg/m^3), 6 h/day, 5 days/week for 5, 14 or 21 days	Adipose gene expression, adipose inflammation, inflammatory cell migration capacity

1

7.1.2.3 Summary

A limited body of epidemiologic and experimental animal studies provide evidence that short-term exposure to $PM_{2.5}$ may affect glucose and insulin homeostasis. However, effects may be transient, so the upstream consequences are somewhat uncertain.

7.1.3 Other Indicators of Metabolic Function

7.1.3.1 Inflammation

Inflammation plays a critical role in the development of T2D and atherosclerosis leading to CHD (Section 7.1.1, CHAPTER 6). As outlined in the Section 7.1.1 (Biological Plausibility), systemic inflammation may promote a peripheral inflammatory response in organs and tissues, such as liver and adipose tissues. Consistent with the 2009 PM ISA, the evidence for systemic inflammation following short-term exposure to $PM_{2.5}$ is limited with some studies reporting changes in markers of inflammation such as the cytokine IL-6 and inflammatory proteins such as CRP while other studies do not show changes in these and other markers. Acute inflammation is transient in nature, inflammatory response is dynamic, and there is technical difficulty in measuring cytokine levels that may be at or below baseline levels, however (Angrish et al., 2016b).

Recent experimental and epidemiologic studies (Section 6.1.11) report at least some evidence of $PM_{2.5}$ mediated effects on systemic inflammation. For example, Behbod et al. (2013) reported that exposure to $PM_{2.5}$ CAP resulted in healthy adults having increased blood leukocytes and neutrophils at 24 hour, but not 3 hour post exposure. In an additional study, Urch et al. (2010) used two different $PM_{2.5}$ CAP exposure levels and reported a statistically significant increase ($p < 0.05$) in blood IL-6 levels following CAP exposure at 3-hour, but not immediately after or the day after exposure. In contrast, Liu et al. (2015) did not report a statistically significant change in Il-6 or CRP. Results from animal toxicology studies reported $PM_{2.5}$ mediated increases in ROS, suggesting oxidative stress (Ito et al., 2008; Seagrave et al., 2008). Evidence in support of systemic inflammation was also provided by a study in which mice exposed to $PM_{2.5}$ CAPs had increased ($p < 0.05$) monocyte chemoattractant protein 1 levels, while Tnf α, and Il 12 were not significantly altered (Xu et al., 2013). Epidemiologic panel studies were similar to CHE and animal toxicology studies in that some of these analyses showed increases in markers of systemic inflammation while others did not (Section 6.1.11.1). Although the above results are seemingly inconsistent, markers of systemic inflammation such as cytokines are often transiently expressed, thus making it difficult to consistently find changes across studies using a variety of methodological approaches (see Section 6.1).

Inflammation of peripheral organs and tissues were reported in animal toxicology studies. Xu et al. (2013) evaluated adipose inflammation concurrently with systemic inflammation in mice exposed to Columbus, OH $PM_{2.5}$ CAPs for 5, 14, or 21 days. The investigators found that the mRNA levels of visceral adipose tissue *Il-6* was increased ($p < 0.05$) at 5 days after exposure, while, no change in *Nos2*, *Tnfα*, *Arg-1*, or *Il-10* were detected (Xu et al., 2013). Furthermore, there was an increase in in the number of macrophages in the epidydimal adipose tissue of $PM_{2.5}$ exposed mice at 5 days ($p < 0.05$) and 21 days ($p < 0.001$) post exposure compared to filtered air controls. A migratory cell assay evaluated and found that the migratory capacity of macrophages ($p < 0.0001$) and neutrophils ($p < 0.05$) was increased, suggesting that $PM_{2.5}$ altered the chemokine composition in visceral adipose tissue (Xu et al., 2013). Sun et al. (2013) provided evidence that $PM_{2.5}$ may exacerbate pre-existing conditions. Specifically, the authors identified increased monocyte/macrophage infiltration in rat epicardial and perirenal adipose tissue that was exacerbated by high fructose diet feeding for 8 weeks prior to exposure as well as oxidative stress (measured by iNOS immunofluorescence) (Sun et al., 2013).

Overall, some studies report increased markers of systemic inflammation following, or in association with, short-term exposure to $PM_{2.5}$. Inconsistency across short-term exposure studies may be related to several factors including the transient nature of the effects. For example, CHE studies examined responses from blood after several hours whereas animal toxicology studies examine responses from blood and other tissues after several days. A limited number of studies provide additional evidence that short-term exposure to $PM_{2.5}$ may result in inflammation of the visceral or perirenal adipose tissue, which is particularly relevant to metabolic function and a risk factor for metabolic syndrome.

7.1.3.2 Liver Function

The liver, which is strategically situated between the portal and systemic circulation, is the site for primary energy and xenobiotic metabolism (Boron and Boulpaep, 2017). Another important liver function is synthesis and degradation of proteins, carbohydrates, and lipids for distribution to extrahepatic tissues depending on energy needs. Finally, the liver regulates whole body cholesterol balance via biliary excretion of cholesterol, cholesterol conversion to bile acids, and by regulating cholesterol synthesis (Boron and Boulpaep, 2017). Consequently, the liver is an essential regulator of whole body metabolism and energy homeostasis.

Acute-phase liver proteins, such as CRP, can act as sensors of liver function and were discussed in more detail in CHAPTER 6, Section 6.2.11. Specifically, there were several epidemiologic studies that found associations between CRP, a protein produced by the liver in response to acute systemic inflammation. These proteins, in combination with other liver enzymes can give information about overall health, including liver function. In a panel study of older adults in Seoul Korea. Kim et al. (2015) reported increases (1−2%) in γ-glutamyl transpeptidase (γ-GTP, a marker of cholestatic function), aspartate aminotransferase (AST, a marker of acute inflammation, not necessarily liver specific) and alanine

aminotransferase (ALT, a marker of liver injury) in association with short-term $PM_{2.5}$ exposure (lag day 3). The mean concentration was 23.2 $\mu g/m^3$ during the study. In contrast, Haberzettl et al. (2016) found no change in the liver enzymes (including AST and ALT) in an animal model.

7.1.3.3 Blood Lipids

7.1.3.3.1 Epidemiologic Studies

Epidemiologic studies of short-term exposure to $PM_{2.5}$ and changes in blood lipids are limited in number. Chen et al. (2016) examined lagged exposure periods from 0–90 days, selecting the period with the best model fit using Akaike Information Criterion (AIC). Short-term (up to 14–day cumulative averages) were associated with changes in HDL to LDL cholesterol ratio, total cholesterol and LDL that were consistent with reduced metabolic function.

7.1.3.3.2 Toxicological Studies

Controlled human exposure studies of metabolic homeostasis are described in Table 7-5. Ramanathan et al. (2016) reported an increasing trend in the HDL oxidant index (HOI) that became significant ($p < 0.05$) when compared to the baseline HOI at 1 hour, but not 20 hours post exposure. These results suggested that PM reduced the antioxidant and anti-inflammatory capacity of HDL particles (Section 6.2.11). Hazucha et al. (2013) identified specific effects on blood lipids and reported a 4.5 and 4.1% decrease ($p < 0.05$) in blood HDL 3 and 22 hours after controlled chamber exposure to $PM_{2.5}$ CAPs in ex- and lifetime smokers. In contrast, short term animal toxicology studies reported no $PM_{2.5}$-mediated effects on blood triglycerides, HDL, LDL, or HDL/LDL ratio (Haberzettl et al., 2016).

Table 7-5 Study specific details from controlled human exposure studies of metabolic homeostasis.

Study	Study Population	Exposure Details	Endpoints Examined
Hazucha et al. (2013).	Current and ex-smokers; n = 11; 3 M, 8 F 35–74 yr	Chapel Hill, NC, 108.7 ± 24.8 $\mu g/m^3$ $PM_{2.5}$ for 2 h at rest	Blood HDL
Ramanathan et al. (2016).	Healthy adults n = 13 M, 17 F; 18–50 yr 28 ± 9	Toronto, Ontario. 148.5 ± 54.4 $\mu g/m^3$ $PM_{2.5}$ (652,259 ± 460,843 particles ≥ 0.3 µm, 2,987 ± 1,918 particles ≥ 2.0 µm) 2 h exposure at rest	HDL antioxidant index

7.1.3.4 Blood Pressure

Short-term $PM_{2.5}$ mediated effects on blood pressure are discussed in detail in the Cardiovascular Chapter (CHAPTER 6, Section 6.1.6). Positive associations between short-term $PM_{2.5}$ exposures and changes in SBP or DBP were not consistently reported in epidemiologic studies. A few CHE studies indicated that $PM_{2.5}$ CAPs may affect BP, however, there were also studies that found no $PM_{2.5}$-mediated effect. Similarly, the animal toxicology studies found little to no $PM_{2.5}$-mediated effects on BP in healthy animals, whereas BP was increased ($p < 0.05$) in the SH rat model (Wagner et al., 2014b), but decreased ($p < 0.05$) in a metabolic disease model (Wagner et al., 2014a). A similar PM exposure mediated an acute decrease ($p < 0.05$) in BP in corpulent JCR rats (Balasubramanian et al., 2013).

7.1.4 Summary and Causality Determination

There were no studies of the effect of short-term $PM_{2.5}$ exposure and metabolic effects reviewed in the 2009 PM ISA (U.S. EPA, 2009). Recent studies provide some evidence supporting effects on glucose and insulin homeostasis and other indicators of metabolic function. Evidence pertaining to the relationship between short-term exposure to $PM_{2.5}$ and metabolic effects is summarized in Table 7-6, using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015).

Recent epidemiologic studies have demonstrated increased FBG, insulin, and HOMA-IR (Lucht et al., 2018a; Peng et al., 2016; Brook et al., 2013b) in association with short-term $PM_{2.5}$ exposure. Yitshak Sade et al. (2016) found no association with blood glucose or lipids and $PM_{2.5}$ exposure, although a positive association between $PM_{2.5}$ exposure (3-month average) and HbA1c, a measure of blood glucose control, was observed. An animal toxicological study provided some evidence for $PM_{2.5}$ impairment of the insulin signaling pathway (Haberzettl et al., 2016). Limited animal toxicology studies provided some evidence for inflammation in the visceral adipose tissue (Xu et al., 2013). Although the controlled human exposure evidence is inconsistent possibly due to the transient nature of inflammation (Section 7.1.3.1), there is epidemiologic evidence of an increase in inflammatory markers in the liver, i.e., γ-GTP, ALT, and AST (Kim et al., 2015). In summary, evidence for a relationship between short-term $PM_{2.5}$ exposure and metabolic effects is based on a small number of epidemiologic and toxicological studies reporting effects on glucose and insulin homeostasis and other indicators of metabolic function such as inflammation in the visceral adipose tissue and liver. **Overall, the collective evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{2.5}$ exposure and metabolic effects.**

Table 7-6 Summary of evidence indicating that the evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{2.5}$ exposure and metabolic effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Evidence of association from a limited number of high quality epidemiologic studies at relevant $PM_{2.5}$ concentrations.	Short term exposures were associated with increased fasting blood glucose, insulin, HOMA-IR and hospitalization for conditions related to diabetes.	†Peng et al. (2016) †Brook et al. (2013b)	1-day mean 10.9 5-day avg 11.5
No consideration of confounding by copollutants.	Epidemiologic studies did not present copollutant models.	Section 7.1.2.1	
Coherence across lines of evidence and related endpoints.	Small number of experimental studies report effects on glucose and insulin homeostasis providing evidence for direct effects on metabolism.	Section 7.1.2.2 Figure 7-2	
Limited biological plausibility.	Small number of studies demonstrating plausibility of pathways involving insulin resistance, systemic inflammation and peripheral inflammation.	Section 7.1.2.2 Section 7.1.3	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

7.2 Long-term $PM_{2.5}$ Exposure and Metabolic Effects

An animal toxicology study (Sun et al., 2009) that showed enhanced insulin resistance, visceral adiposity, and adipose inflammation in a diet-induced obesity mouse model was reviewed in the 2009 PM ISA. In the present ISA, multiple epidemiologic and experimental studies of glucose and insulin homeostasis and diabetes, as well as other outcomes are available for review. Overall, there is evidence from some studies that long-term exposure to $PM_{2.5}$ can affect glucose and insulin homeostasis but prospective epidemiologic studies do not report consistent positive associations with the incidence of T2D.

The discussion of long-term $PM_{2.5}$ exposure and metabolic effects opens with a discussion of biological plausibility (Section 7.2.1) that provides background for the subsequent sections in which groups of related endpoints are presented in the context of relevant disease pathways. These outcome groupings are metabolic syndrome (Section 7.2.2), glucose and insulin homeostasis (Section 7.2.3), T2D

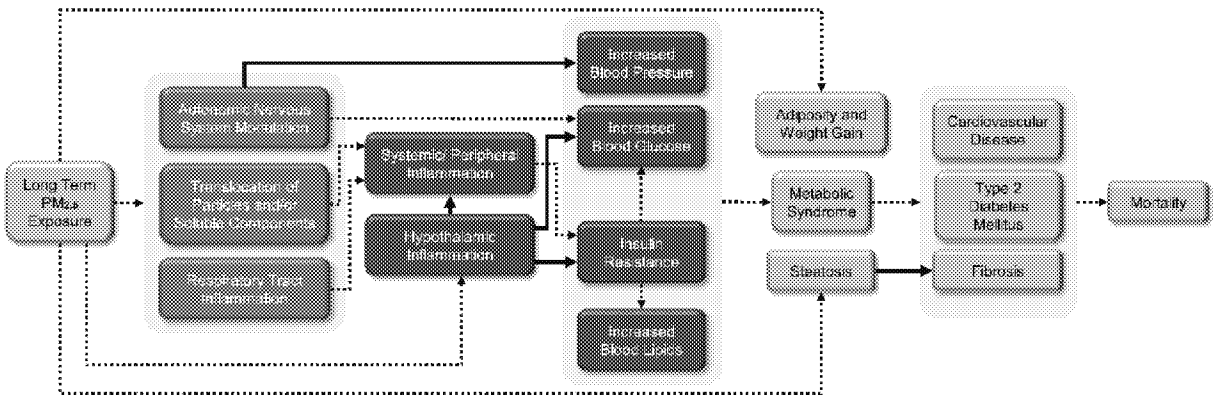
(Section 7.2.4), and other indicators of metabolic function (Section 7.2.5). Gestational diabetes and Type 1 diabetes are discussed in Section 7.2.6 and Section 7.2.7, respectively. Summary discussion for $PM_{2.5}$ components (Section 7.2.8), copollutant confounding (Section 7.2.9) and metabolic disease mortality (Section 7.2.10) follow. The collective body of evidence is integrated across and within scientific disciplines[69], and the rationale for the causality determination is outlined in Section 7.2.11.

7.2.1 Biological Plausibility

This section describes biological pathways that potentially underlie metabolic health effects resulting from long-term exposure to $PM_{2.5}$. Figure 7-3 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" exposure to $PM_{2.5}$ may lead to metabolic health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 7.2.

The health sections below include numerous new long-term $PM_{2.5}$ exposure studies that further inform the potential pathways leading to metabolic effects. In the short-term $PM_{2.5}$ biological plausibility (Section 7.1.1) potential pathways were described that implicitly support proposed relationships between short term $PM_{2.5}$-mediated biological effects that collectively alter energy homeostasis to promote metabolic syndrome. New evidence gleaned from long-term $PM_{2.5}$ exposure studies expands the evidence pertaining to biological plausibility as well as our implicit understanding of the pathological continuum underlying metabolic disease development and progression. Specifically, the long-term exposure studies inform disease onset or longitudinal changes in measured endpoints that cannot be ascertained through the application of a short-term exposure study design. Furthermore, in some experimental studies, endpoints observed in short-term exposure studies are part of a long-term study and, therefore, do not include evidence gathered at animal sacrifice. Expansion of the pathways described in Section 7.1 are supported not only by the long-term exposure evidence described in this section, but also experimental and observational evidence described in the dosimetry, pulmonary, nervous system, and cardiovascular chapters (CHAPTER 4, CHAPTER 5, CHAPTER 6, and CHAPTER 8, respectively).

[69] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations unless otherwise noted.



The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 7-3 Potential biological pathways for metabolic effects following long-term $PM_{2.5}$ exposure.

Inhalation of $PM_{2.5}$ may initiate pathways that include ANS activation, translocation of particles and/or soluble components, and respiratory tract inflammation that converge upon inflammation leading to insulin resistance (previously described in Section 7.1.1). The long-term exposure toxicological evidence from inhibitor studies in diabetic mouse models (Section 7.2.3.2) provide important evidence for connecting these initial pathways to metabolic syndrome risk factors and clinical outcomes. Aside from inflammatory mediator diffusion from the lung into the systemic circulation, inhibitor studies in a diabetic mouse model provide evidence that increased hypothalamic inflammation, mediated by the NFκβ signaling pathway, is sufficient to promote long term $PM_{2.5}$ mediated glucose intolerance, insulin resistance, increases in circulating inflammatory monocytes, and increases in inflammatory gene expression in peripheral tissues including liver, adipose, and heart (Zhao et al., 2015; Liu et al., 2014b) (CHAPTER 6 and CHAPTER 8). The convergence of these pathways on glucose and insulin disruption is notable since multiple studies, albeit from the same group of investigators evaluating $PM_{2.5}$ CAPs collected from the same Columbus, OH air shed, identified that long-term $PM_{2.5}$ exposure elicited insulin resistance and increased blood glucose/glucose intolerance in healthy mice (Section 7.2.3.2). Further molecular analysis of proteins involved in the NFκβ and insulin signaling pathways consistently showed that long-term $PM_{2.5}$ exposure decreased Akt phosphorylation in tissues including liver, adipose, heart, and skeletal muscle (Section 7.2.5.1), providing a potential connection between inflammatory mediator diffusion in the circulatory system leading to peripheral organ/tissue inflammation and insulin resistance. Zheng et al. (2013) indicated these effects were possibly mediated by activation of Toll-like receptor 4 (TLR4), c-Jun N-terminal kinase (JNK) and NFκβ, leading to suppression of the insulin-receptor substrate

1 (IRS-1) signaling and, consequently, decreased Akt phosphorylation leading to impaired insulin
2 signaling. These findings are consistent with the decreased Akt phosphorylation finding after short term
3 $PM_{2.5}$ exposure to CAPs collected from the Louisville, KY air shed (Haberzettl et al., 2016) and support a
4 continuum for $PM_{2.5}$ metabolic effects on insulin resistance.

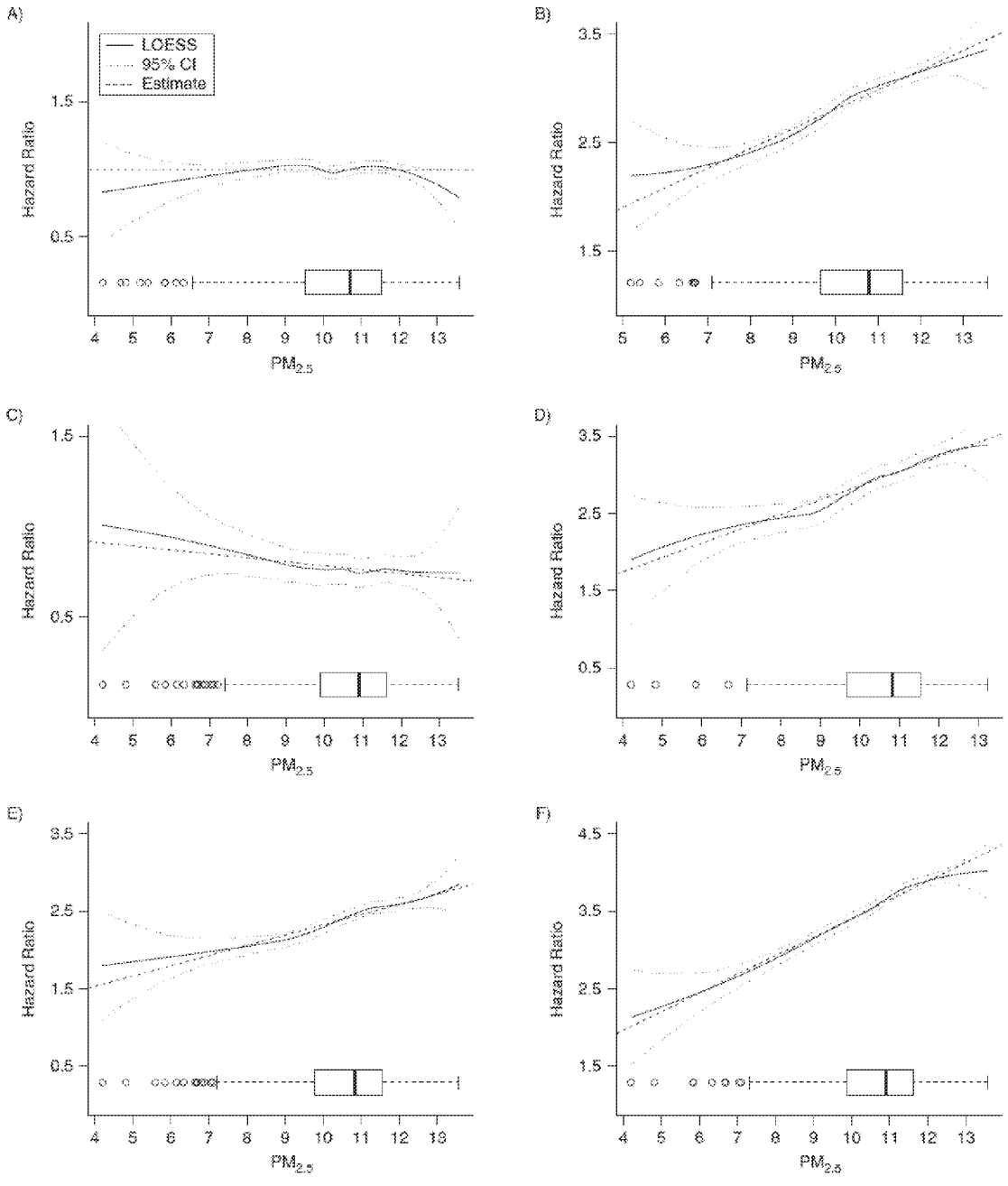
5 In addition to the immune activation and NFκβ signaling pathways discussed above, evidence
6 from genetic knockout models also supports roles for TLR4 and NADPH oxidase pathways leading to
7 monocyte recruitment and inflammation. Mice with nonfunctional neutrophil NADPH oxidase activity,
8 which is required for superoxide anion production, were protected from $PM_{2.5}$-induced increases in
9 superoxide production (Kampfrath et al., 2011), insulin resistance, increase in abdominal mass and
10 visceral adiposity, and fibrosis in mice (Zheng et al., 2015; Xu et al., 2010). Kampfrath et al. (2011)
11 found that genetic knockout of *Tlr4* protected mice from $PM_{2.5}$-mediated increases in circulating
12 monocytes and prevented phosphorylation of the $p47^{phox}$ subunit that is required for NADPH oxidase
13 activity and superoxide production. Yet, while superoxide was attenuated in *Tlr4* deficient mice, it
14 remained induced in monocytes, aorta, and perivascular fat (Kampfrath et al., 2011). Mice with a
15 nonfunctional CC-chemokine receptor 2 (CCR2), with a phenotype of defective monocyte requirement
16 during immune responses, were protected from $PM_{2.5}$ and high fat diet induction of hepatic steatosis,
17 insulin resistance, and systemic and peripheral inflammation (Liu et al., 2014c). Although no association
18 was found in a cross-sectional study between long-term $PM_{2.5}$ exposure and steatosis (Li et al., 2016),
19 hepatic steatosis and fibrosis were found in mice exposed long-term to $PM_{2.5}$ (Section 7.2.5.2).

20 As described here, there are proposed pathways by which long-term exposure to $PM_{2.5}$ could lead
21 to metabolic health effects. One pathway involves ANS modulation, translocation of particulates and/or
22 soluble components, and respiratory tract inflammation that may lead to systemic and peripheral
23 inflammation that is linked to insulin resistance and metabolic syndrome comorbidities. While
24 experimental studies involving animals contribute most of the evidence of upstream effects,
25 epidemiologic studies found associations of long-term $PM_{2.5}$ exposure with metabolic syndrome
26 (Section 7.2.2), insulin resistance and glucose tolerance (Section 7.2.3), T2D (Section 7.2.4),
27 cardiovascular disease (Chapter 6), and metabolic disease mortality (Section 7.2.10). The pathways
28 leading to these outcomes are not without gaps (e.g., the pathways to hypothalamic inflammation,
29 steatosis, adiposity and weight gain); however, they provide coherence and biological plausibility for the
30 evidence streams supporting metabolic health effects and will be used to support the causal determination,
31 which is discussed later in the chapter (Section 7.2.11).

7.2.2 Metabolic Syndrome

32 The criteria for a diagnosis of metabolic syndrome, which are summarized in Table 7-1, include
33 changes in glucose and insulin homeostasis, obesity, increased blood pressure, and increased triglyceride
34 levels. Although most available studies focus on individual components of metabolic syndrome, most

commonly glucose and insulin homeostasis (Section 7.2.3), the association of long-term exposure to $PM_{2.5}$ with a diagnosis of metabolic syndrome was examined in an epidemiologic study (Table 7-6). In this study, older adult, male, participants of the Normative Aging Study (NAS) were followed between 1993 and 2011. Associations with the incidence of newly diagnosed metabolic syndrome [HR: 3.30 (95% CI: 1.34, 8.11)] and several of its components including FBG ≥100 mg/dL [HR: 2.49 (95% CI: 1.16, 5.19)], blood pressure ≥130/85 mmHg [HR 2.49 (95% CI: 0.86, 7.34)], increased triglycerides ≥150 mg/dL [HR: 1.93 (95% CI: 1.00, 3.71)] were reported (Wallwork et al., 2017). Wallwork et al. (2017) also examined the C-R relationship between long-term $PM_{2.5}$ exposure and the hazard for metabolic syndrome and its components (Figure 7-4). No major departures from linearity were apparent and HRs remained significant and strengthened in a sensitivity analysis restricted to 1-year average $PM_{2.5}$ concentrations <12 $\mu g/m^3$.



(A) Abdominal Obesity; (B) high fasting blood glucose (C) low high-density lipoprotein cholesterol; (D) hypertension; (E) hypertriglyceridemia; (F) metabolic syndrome.

Source: Permission pending, Wallwork et al. (2017).

Figure 7-4 Locally weighted scatterplot smoothing (LOESS) regression of hazard ratios on $PM_{2.5}$ concentration. Composite diagnosis of metabolic syndrome and each individual component according to the level of exposure among older adult males in the Normative Aging Study.

7.2.3 Glucose and Insulin Homeostasis

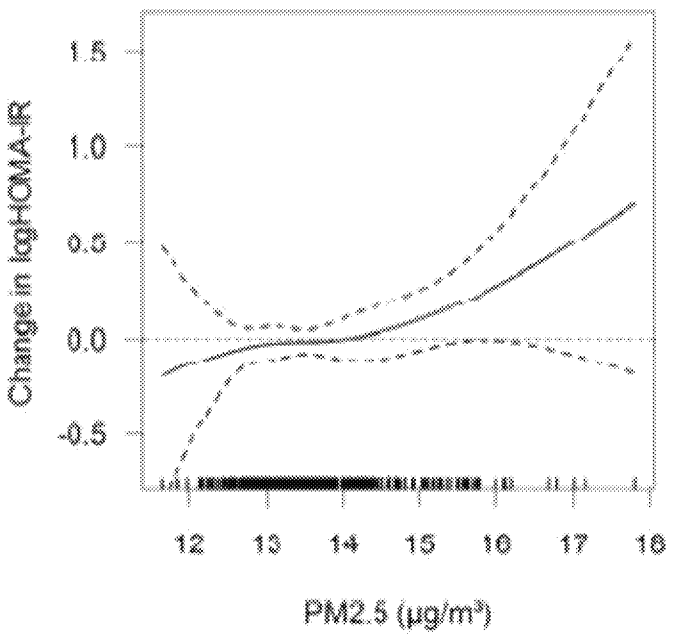
As discussed in the introduction to the metabolic effects chapter (Section 7.1), insulin regulates glucose homeostasis. There was one animal toxicology study (Sun et al., 2009) that showed enhanced insulin resistance in a diet-induced obesity mouse model in the 2009 PM ISA. Several recent studies on this topic add to the overall evidence. Endpoints examined in these studies include FBG, HbA1c, and insulin resistance (e.g., the homeostatic model assessment of insulin-resistance [HOMA-IR]). Recent epidemiologic and experimental provide generally consistent evidence supporting the effect of long-term $PM_{2.5}$ exposure on glucose and insulin homeostasis.

7.2.3.1 Epidemiologic Studies

The epidemiologic studies of the association between long-term $PM_{2.5}$ exposure and glucose and insulin homeostasis are described in Table 7-6. Lucht et al. (2018b) conducted a longitudinal analysis of nondiabetic participants of the HNR reporting an association of 91-day average exposure to $PM_{2.5}$ with increased HbA1c. In this study $PM_{2.5}$ exposure was associated with 0.09% increase in HbA1c (95% CI: 0.05, 0.13) in the main model, which was adjusted for an array of covariates including BMI, physical activity, smoking, neighborhood-level unemployment.

Several cross-sectional epidemiologic studies of glucose and insulin homeostasis provide support for the findings from this longitudinal study. Chen et al. (2016) analyzed the effect of both short- (0–90-day lags) and long-term exposure to $PM_{2.5}$ on glucose homeostasis in Mexican American women with a history of gestational diabetes (GMD) and their family members (BetaGene study). Subjects with a FBG level <7 mmol/L were assessed using detailed measurements of insulin sensitivity and secretion from a frequently sampled intra-venous glucose tolerance test (FSIGT). Cumulative exposure to $PM_{2.5}$ (lags up to 60 days) and annual average $PM_{2.5}$ were associated with several measures of insulin resistance, higher fasting blood glucose and indicators of dyslipidemia in this study. Associations with $PM_{2.5}$ persisted after adjustment for NO_2.

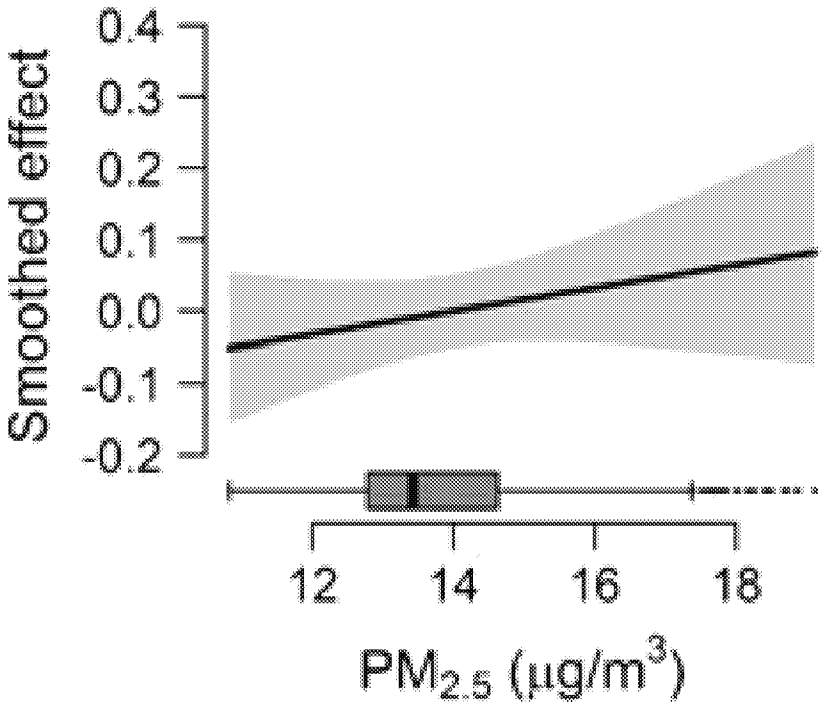
Wolf et al. (2016) reported increases, although CIs were wide, in HOMA-IR [17.32% (95% CI: −2.32, 39.11)], glucose [2.86% (95% CI; 0.00, 5.89)], insulin [14.82% (95% CI: −3.57, 35.00)], as well as Leptin and CRP in association with long-term exposure to $PM_{2.5}$ in a cross-sectional analysis of a German cohort (KORA). HOMA IR was log-transformed in the analysis due to a deviation from linearity (Figure 7-5). In another study, Yitshak Sade et al. (2016) examined short-term (Section 7.1.2) and 3-month average exposures to serum glucose, HbA1c, and lipids, reporting an association between 3-month average $PM_{2.5}$ exposure and HbA1c, an indicator of diabetes control, among those with diabetes [2.09% (95% CI: 0.25, 3.99)]. Chuang et al. (2011) reported associations of 1-year average $PM_{2.5}$ concentration with blood lipid and glucose levels in a cross-sectional study in Taiwan. Liu et al. (2016) found cross-sectional positive associations of long-term $PM_{2.5}$ concentration with FBG [0.03 nmol/L (95% CI: 0.02, 0.04)] and HbA1c (0.01% 95% CI: 0.01, 0.01) in a study of retired adults in China [Note: these results have been standardized to 5 μg/m^3 but were originally presented per IQR (41.1 μg/m^3) increase in $PM_{2.5}$ concentration.].



Source Wolf et al. (2016).

Figure 7-5 Concentration response function for $PM_{2.5}$ using restricted cubic spline with three degrees of freedom (adjusted for age, sex, body mass index (BMI), waist-hip ratio, smoking status, and month of blood draw).

Effects on glucose homeostasis in children are also observed in epidemiologic studies. Toledo-Corral et al. (2018) enrolled obese and overweight African-American and Latino children between 8 and 18 years of age to study the effect of long-term exposure to $PM_{2.5}$ on measures of glucose metabolism. $PM_{2.5}$ concentrations were associated with a metabolic profile that indicates an increased risk of developing T2D (i.e., fasting insulin, lower insulin sensitivity, higher acute insulin response to glucose and increased FBG) in this cross-sectional analysis. Thiering et al. (2013) reported an association between $PM_{2.5}$ concentration estimated at the residence using LUR and an increase in HOMA-IR at age 10, among participants in the GINIplus and LISAplus birth cohorts [27.7% (95% CI: −3.5, 66.2)]. In a subsequent analysis of a larger sample of children at age 15 years old (Thiering et al., 2016), a comparable increase in HOMA-IR was observed [16.59% (95% CI: −2.84, 39.32)]; however, the effect was attenuated in copollutant models that adjusted for NO_2 [4.43% (−14.77, 27.50)]. The authors also examined the C-R relationship (Figure 7-6) reporting no statistical evidence that the relationship between long-term $PM_{2.5}$ exposure and HOMA-IR deviated from linearity.



Note: Box plots on the *x*-axis show the distribution of $PM_{2.5}$ concentration.
Source: Permission pending, Thiering et al. (2013).

Figure 7-6 Smoothed associations between insulin resistance and long-term $PM_{2.5}$ exposure assessed using generalized additive models adjusted for sex, age and body mass index (BMI).

7.2.3.2 Toxicological Studies

The effects of long-term $PM_{2.5}$ on glucose homeostasis (e.g., glucose tolerance test, insulin tolerance test, fasting glucose and insulin, blood glucose and insulin levels, and the HOMA-IR) were demonstrated in several studies of experimental animals (Table 7-7). Increased ($p < 0.05$) blood glucose levels and/or glucose intolerance and increased HOMA-IR in wild-type animals eating a normal chow diet and exposed (long-term, ≥30 days) to $PM_{2.5}$ compared to controls, was shown in studies from two laboratories [Figure 7-7 (Liu et al., 2014c; Liu et al., 2014a; Zheng et al., 2013; Xu et al., 2011a; Xu et al., 2010)]. In contrast, Haberzettl et al. (2016) showed no increased in glucose levels in mice and Yan et al. (2014) found no HOMA-IR effects in rats after $PM_{2.5}$ exposure. The molecular evidence consistently suggested that long-term $PM_{2.5}$ exposure disrupted the insulin signaling pathway by inhibition of IRS1 signaling leading to decreased ($p < 0.05$) peripheral Akt phosphorylation in the liver (Liu et al., 2014a; Zheng et al., 2013; Xu et al., 2011a) and aorta (Haberzettl et al., 2016) of mice (see Section 7.2.5.1).

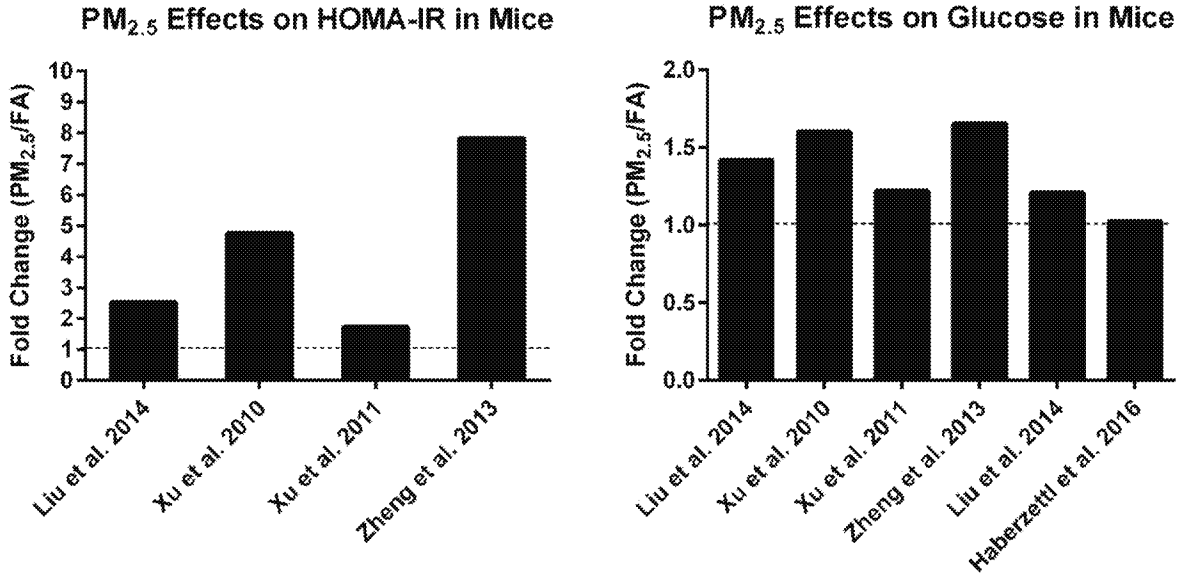


Figure 7-7 $PM_{2.5}$ effects on insulin resistance and glucose tolerance in mice exposed to 19.6–139 µg/m^3 $PM_{2.5}$ for 30 days to 17 weeks.

Stages of diabetes progression include prediabetes, which is characterized by impaired glucose tolerance and/or decreased insulin sensitivity, an initial phase (Phase 1) in which pancreatic beta cells become dysfunctional, and a second phase (Phase 2), which is characterized by fasting hyperglycemia and beta cell atrophy. In the end stage (Phase 3) of the disease, the pancreatic cells no longer release insulin.

Table 7-7 Epidemiologic studies of long-term exposure to $PM_{2.5}$ and glucose and insulin homeostasis.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Wallwork et al. (2017) Boston, MA Longitudinal $PM_{2.5}$: 2000–2011 Outcome: 1993–2011	NAS N = 587 Older adult males	Annual avg prior to clinic visit, spatio-temporal model incorporating LUR and satellite derived AOD (10 × 10 km and 1 × 1 km grids), C-V R^2 = 0.81 and 0.87 depending on resolution	Mean: 10.5 (SD: 1.4) Range: 4.2–13.6	Metabolic syndrome and its components (Table 7-1)	Correlations (*r*): NR Copollutant models: NR
Lucht et al. (2018b) Ruhr area, Germany Longitudinal $PM_{2.5}$ Outcome: 2000–2008	HNR study N = 4,176 Nondiabetic	EURAD model, 1 km grid cell *r* = 0.51–0.61, modeled and measured concentrations (Wurzler et al., 2004)	Mean = 17.6 IQR = 4	Blood glucose level	Correlations (*r*): *r* = 0.82 NO_2; *r* = 0.47 PN_{AM} Copollutant models: NR
†Chen et al. (2016) Southern CA Cross-sectional $PM_{2.5}$: 2002–2008 Outcome: 2002–2008	BetaGene study N = 1,023 Mexican-American women with history of GDM	Spatial interpolation (inverse distance weighted, IDW) of monitor concentrations within 50 km	Mean(SD): 16.8 (5.5)	Insulin sensitivity and secretion using FSIGT, oGTT, blood lipids (see Section 7.1.3.3)	Correlations (*r*): NO_2 *r* = 0.56, Ozone *r* = −0.07 copollutant model: positive after adjustment for NO_2
†Wolf et al. (2016) Augsburg and two adjacent rural counties, Germany Cross-sectional $PM_{2.5}$: 2008–2009 2006–2008	KORA N = 2,944 Mean age: 56.2 yr	Annual avg, LUR, at residence (ESCAPE protocol)	Mean (SD) 13.5–13.6 (0.8–0.9)	HOMA-IR, Glucose, Insulin, HbA1c, Leptin, hs-CRP	Correlations (*r*): $PM_{10-2.5}$ *r* = 0.32, NO_2 *r* = 0.45 copollutant models: NR
†Yitshak Sade et al. (2016) Retrospective cohort $PM_{2.5}$: 2003–2012 Outcome: 2003–2012	N = 73,117	3-mo avg, satellite derived AOD with LUR, C-V R^2 0.72	Mean 22.3	HbA1c LDL HDL Triglycerides	Correlations (*r*): NR Copollutant models: NR

Table 7-7 (Continued): Epidemiologic studies of long-term exposure to $PM_{2.5}$ and glucose and insulin homeostasis.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Chuang et al. (2011) Taiwan Cross-sectional $PM_{2.5}$: 2000	Biomarkers of Aging Study N = 1,023	Annual avg (2000)	Mean (SD): 35.31 (15.9) IQR 20.42	FBG, HbA1c (lipids, BP)	Correlations (*r*): NR Copollutant models: NR
†Liu et al. (2016) China Cross-sectional $PM_{2.5}$/Outcome: June 2011–Mar 2012	Retirement Longitudinal study N = 11,847	Avg (2011–2012) at residence, satellite derived AOD and monitors (10 × 10 km)	Mean 72.6 (SD:27.3) IQR: 41.1	FBG HbA1c	Correlations (*r*): NR Copollutant models: NR
†Toledo-Corral et al. (2018) Los Angeles, CA Cross-sectional 2001–2012	N = 429 overweight and obese children 8–18	1–12 mo exposure prior to clinic visit at geocoded address	Mean (SD): 17.8 (5.2)	Glucose metabolism: FBG, fasting insulin, HOMA-IR, insulin sensitivity, acute insulin response	Correlations (*r*): NR Copollutant models: NR
†Thiering et al. (2013) Munich, Wesel, and South Germany Cross-sectional $PM_{2.5}$: 2008–2009	GINIplus and LISAplus N = 397 Children, age 10 yr	Annual avg at residence, LUR (Eeftens et al., 2012)	Mean 14 (SD: 1.9)	HOMA-IR	Correlations (*r*): NR Copollutant models: NR
†Thiering et al. (2016) Munich, Wesel, and South Germany Cross-sectional $PM_{2.5}$: 2008–2009	GINIplus and LISAplus N = 837 Adolescents, 15 yr	Annual avg at residence, LUR [see (Eeftens et al., 2012)]	Mean 15.1 (SD: 2.2)	HOMA-IR	copollutant model: attenuated after adjustment by NO_2

AOD = Aerosol Optical Density; Avg = average; EURAD = European Air Pollution Dispersion; FBG = fasting blood glucose; FSIGT = frequently sampled intra-venous glucose tolerance; GDM = gestational diabetes mellitus; GINIplus = German Infant Study on the Influence of Nutrition Intervention plus Environmental and Genetic Influences on Allergy Development; HbA1c = Glycated Hemoglobin; HOMA-IR = homeostasis model assessment of insulin resistance; LISAplus = Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics; LUR = land use regression; oGTT = oral glucose tolerance test; NR = not reported; KORA = Cooperative Health Research I the Region of Augsburg; C-V = Cross Validation.

†Studies published since the 2009 PM ISA.

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There are several animal models available to evaluate diabetes progression including those that rely on diet to recapitulate prediabetes and diabetes-like phenotypes, KK-Ay mouse models of Phase 1 to 3 diabetes, and a streptozotocin-induced diabetic model, which selectively destroys the pancreatic islet β-cells resulting in a pathology like T1D in humans. Mouse models may present with varying degrees of obesity.

Recent studies of diabetes progression support the findings in animal toxicological studies of glucose homeostasis in wild-type animals fed normal chow (Table 7-8). In the diet-induced mouse models of diabetes Xu et al. (2010) and Liu et al. (2014c) found impaired ($p < 0.05$) glucose tolerance and/or insulin sensitivity independent of diet in mice exposed to $PM_{2.5}$ exposure for 10 and 17 weeks. Haberzettl et al. (2016) similarly fed animals a high fat diet, but found that 30-day exposure to $PM_{2.5}$ did not affect insulin resistance or glucose homeostasis. In contrast to the dietary models, the KK-Ay mouse model (for Phase 1−3 diabetes) developed hyperglycemia ($p < 0.05$) as soon as 5 weeks after $PM_{2.5}$ exposure, and the effects persisted 8-weeks after exposure, whereas insulin resistance (measured by HOMA-IR) was identified at 1, 3, and 8 weeks after CAPs exposure (Liu et al., 2014b). However, in a similar study Liu et al. (2014a) found glucose intolerance and insulin resistance 5 weeks after $PM_{2.5}$ exposure, but not 8 weeks after exposure. There was evidence from both models indicating that $PM_{2.5}$ caused inflammation (Section 7.2.5.1). Specifically, although $PM_{2.5}$ exposure and high fat diet did not interact to affect glucose tolerance or insulin resistance (discussed above), inflammation was worsened ($p < 0.05$) by high fat diets (Xu et al., 2010). In the KK-Ay mouse study Liu et al. (2014b) investigated the role of hypothalamic inflammation in T2DM. In two separate experiments Liu et al. (2014b) administered either a TNFα or IKKβ inhibitor into the intra-cerebroventricular region of KK-Ay mice. TNFα is an inflammatory cytokine and IKKβ binds cytosolic NF-κβ preventing NF-κβ translocation to the nucleus and regulation of inflammatory gene expression. TNFα inhibition had no effect on glucose tolerance or insulin sensitivity, however IKKβ inhibition ameliorated PM effects on GTT and ITT ($p < 0.05$). These results indicate a role for nervous system effects, specifically hypothalamic NF-κβ signaling, in regulating inflammation and energy homeostasis and are further discussed in the chapter on Nervous System Effects (Chapter 8).

Table 7-8 Study specific details from animal toxicology studies of glucose and insulin homeostasis.

Study	Study Population	Exposure Details	Endpoints Examined
Haberzettl et al. (2016)	Mouse, male, C57BL/6J, ND or HFD, 8–12 weeks, n = 4–8	Columbus, OH CAPs, $PM_{2.5}$; 30–100 µg/m^3 Group 1: exposed for 6 h/day for 9 or 30 days. Group 2: treated with daily dose of water, metformin 50 mg/kg dose 2 days before, 100 mg/kg dose 1 day before and 300 mg/kg at the time of, or 1 mg/kg rosiglitazone 2 mg/kg two days before 9 days CAP exposure in drinking water.	Body weight, fasting blood glucose and insulin, HOMA-IR, organ weights, blood lipids, liver clinical chemistry, insulin signaling pathway, circulating bone marrow derived stem cells.
Liu et al. (2014c)	Mouse, male, C57BL/6 and Ccr2$^{-/-}$ (inflammation model), ND or HFD, 18 weeks, WT-FA (n = 8), WT-PM (n = 9), CCR2-FA (n = 9), CCR2-PM (n = 8)	Columbus, OH CAPs, $PM_{2.5}$; 116.9 µg/m^3; 6 h/day, 5 days/week for 17 weeks, whole body inhalation.	Body weight, glucose tolerance test, HOMA-IR, inflammation, liver and plasma lipids, vasorelaxation, macrophage infiltration, intra-vital leukocyte-endothelial interactions in adipose and muscle.
Liu et al. (2014a)	Mouse, male, KK-Ay, 5 weeks old	Columbus, OH CAPs, $PM_{2.5}$; 100 µg/m^3, 6 h/day, 5 days/week, 5 weeks or 8 weeks	Body weight, oxygen consumption, CO_2 production, thermogenesis, spleen mass, blood cytokine, hepatic Akt phosphorylation, glucose homeostasis, adiponectin and leptin, adipose tissue p38 and ERK phosphorylation.
Liu et al. (2014b)	Mouse, KK-Ay (develop diabetes and overweightness), 5 or 7 weeks old, sex not reported Exposure 1 (n = 7–8/group), Exposure 2 (n = 6/group), Exposure 3 IMD-0354 group n = 8, infliximab group n = 6	Columbus, OH CAPs, $PM_{2.5}$ Exposure 1: 116.9 µg/m^3 for 6 h/day, 5 days/week, 5 weeks or 8 weeks Exposure 2: 139.5 µg/m^3 + infliximab (TNFα antibody) or artificial CSF for 6 h/day, 5 days/week, 5 weeks Exposure 3: CAPs $PM_{2.5}$ 73.6 µg/m^3 + IMD-0354 (IKKB inhibitor) or DMSO for 6 h/day, 5 days/week, 4 weeks	Exposure 1: Fasting blood glucose, HOMA-IR, hypothalamus TNFα, IL-6 and IKKB mRNA levels, oxidized PAPC. Exposure 2: Hypothalamic TNFα antagonism, GTT, ITT, thermogenesis, body weight. Exposure 3: IKKB inhibition IKK-NFkB pathway upregulation normalized PM effects on GTT and ITT, circulating monocytes ($p = 0.0616$), and visceral adipose monocytes ($p < 0.05$) compared to PM controls. Body weight, food intake, glucose tolerance test, insulin levels, HOMA-IR, oxygen consumption, heat production, inflammation, inhibition of the cerebroventricular NFκβ pathway, insulin signaling pathway.
Xu et al. (2010)	Mouse, male, ND or high fat (HFD), wild-type or *p47$^{phox-/-}$* ND, 3 weeks, n = 16/group	Columbus, OH CAPs, $PM_{2.5}$; diet study: 111.0 µg/m^3; 6 h/day, 5 days/week for 10 weeks, whole body inhalation	Glucose tolerance test, HOMA-IR, inflammatory markers and inflammation, adiposity, and vasomotor responses

Table 7-8 (Continued): Study specific details from animal toxicology studies of glucose and insulin homeostasis.

Study	Study Population	Exposure Details	Endpoints Examined
Xu et al. (2011a)	Mouse, male, C57BL/6, ND, 4 weeks, n = 11 FA, n = 9 $PM_{2.5}$	Columbus, OH CAPs, $PM_{2.5}$; 94.4 µg/m^3; 6 h/day, 5 days/week for 10 mo, whole body inhalation.	Body and adipose depot weights, glucose tolerance test, HOMA-IR, systemic inflammation, adipokines, mitochondrial size and number, gene expression, superoxide production/oxidative stress/Nrf2 signaling, insulin signaling pathway.
Yan et al. (2014)	Rat, male, Sprague Dawley T1D (streptozotocin induced), 14 weeks, n = 8	Taipei Air Pollution Exposure System for Health Effects (TAPES) filtered for $PM_{2.5}$; 13.3 µg/m^3, 24 h/day, 7 days/week, for 16 weeks, whole body inhalation.	Glucose/insulin/serum lipids, HOMA-IR, inflammatory and renal function blood biomarkers, urinary protein excretion, histopathology (heart, aorta, and kidney).
Yan et al. (2014)	Rat, male, Sprague Dawley T1D (streptozotocin induced), 14 weeks, n = 8	Taipei Air Pollution Exposure System for Health Effects (TAPES) filtered for $PM_{2.5}$; 13.3 µg/m^3, 24 h/day, 7 days/week, for 16 weeks, whole body inhalation.	Glucose/insulin/serum lipids, HOMA-IR, inflammatory and renal function blood biomarkers, urinary protein excretion, histopathology (heart, aorta, and kidney).

7.2.3.3 Summary

A longitudinal study of older adults in the Boston-area that reported associations of long-term $PM_{2.5}$ with metabolic syndrome and several of its components and another longitudinal study reported an effect on HbA1c among those without diabetes. Multiple cross-sectional epidemiologic studies supported these findings but epidemiologic studies generally did not consider confounding by copollutants. Coherence with the epidemiologic findings was provided by findings from some animal toxicological studies that demonstrated increased blood glucose levels, glucose intolerance and increased HOMA-IR in wild-type animals eating a normal chow diet following long-term exposure to $PM_{2.5}$ compared to controls (Figure 7-7). Limited support for these findings was provided by studies of animal models of diabetes progression.

7.2.4 Type 2 Diabetes Mellitus

Type 2 Diabetes (T2D) Mellitus is an endocrine disorder characterized by high blood glucose levels (i.e., fasting blood glucose ≥126 mg per dL) and insulin resistance. There were no studies of long-term $PM_{2.5}$ exposure and diabetes reviewed in the 2009 PM ISA (U.S. EPA, 2009). Multiple recent studies examine the association of long-term exposure to $PM_{2.5}$ with diabetes in adult populations. Most of the epidemiologic studies are longitudinal in design and have been conducted in well-established cohorts in the U.S. (e.g., Multi-Ethnic Study of Atherosclerosis [MESA] Air, Black Women's Health Study [BWHS], Nurses' Health Study [NHS], and Health Professional Follow-up Study [HPFS]). The

collective epidemiologic and toxicological evidence described below provide a basis for long-term $PM_{2.5}$ exposures leading to impaired glucose and insulin homeostasis and diabetes. Although findings across epidemiologic studies were not consistent, some high quality, longitudinal studies reported positive associations between long-term exposure to $PM_{2.5}$ and the incidence of diabetes. In addition, there is toxicological evidence that found PM exacerbated glucose tolerance in mouse models of diabetes.

7.2.4.1 Epidemiologic Studies of Type 2 Diabetes Mellitus

Prospective studies do not consistently report positive associations between long-term $PM_{2.5}$ exposure and incident diabetes (Table 7-6, Table 7-9).

Studies used a variety of outcome ascertainment methods ranging from self-reported diabetes to confirmed FBG level. Although some studies did not explicitly distinguish between T1D and T2D, most studies focused on incident cases among adults, which are generally cases of T2D. Park et al. (2015) examined the association of long-term $PM_{2.5}$ exposure and diabetes in MESA Air participants (n = 5,135) who were free of the disease at their baseline exam. These investigators observed a positive but imprecise (i.e., wide confidence intervals) association with diabetes [HR: 1.11 (95% CI: 0.75, 1.61)]. Stratified analyses showed that the association between $PM_{2.5}$ and diabetes was present among women [HR: 1.22 (95% CI: 0.72, 2.03)] but not among men [HR: 1.00 (95% CI: 0.55, 1.77)]. Adjustment for covariates, including neighborhood-level SES and site, increased the magnitude of the effect estimates observed in this study. Unlike in the MESA cohort, sex-specific estimates for the association with incident diabetes were similar among female nurses and male health professionals in the study by Puett et al. (2011) where a positive but imprecise association was observed in the population overall [HR: 1.04 (95% CI: 0.95, 1.13)]. The association with $PM_{2.5}$ was unchanged after adjustment for neighborhood level SES (quantitative results not presented) but diminished in copollutant models adjusting for $PM_{10-2.5}$ (Puett et al., 2011).

In an analysis of Los Angeles residents in black women's health study (BWHS) who were followed from 1995 through 2005, Coogan et al. (2012) observed a positive association [HR: 1.28 (95% CI: 0.88, 1.85)] with a wide CI. In an extended analysis of the full BWHS cohort that included women residing in 56 metropolitan areas, followed from 2005 through 2011, Coogan et al. (2016) reported no association [HR: 0.98 (95% CI: 0.83, 1.16)], however. The preliminary analysis of Coogan et al. (2012) reported substantial attenuation in the association of $PM_{2.5}$ with diabetes after adjustment for NO_X (copollutant confounding was not evaluated in the 2016 study because a null association with $PM_{2.5}$ was observed). In a sensitivity analysis of Los Angeles residents followed through 2011 that allowed comparison to the previous findings, the HR was positive but attenuated and the CI was relatively wide (Coogan et al., 2016).

Table 7-9 Epidemiologic studies of long-term exposure to $PM_{2.5}$ and diabetes.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Park et al. (2015) Longitudinal cohort $PM_{2.5}$: 2000 Outcome: 2000–2012	MESA N = 5,135	Annual avg at residence, spatio-temporal model [see Sampson et al. (2011)]	Mean 17.3 (SD 3.1) in people with diabetes (baseline) Mean 16.7 (SD: 2.8) in people without diabetes	Use of diabetes medication or fasting glucose ≥126 mg/dL	Correlation (*r*), NO_X = 0.69 Copollutant model: NR
†Puett et al. (2011) Longitudinal cohort U.S. $PM_{2.5}$: 12 mo prior to diagnosis Outcome NHS: 1976–2009 Outcome HPFS: 1986–2009	NHS (N = 74,412) and HPFS (N = 15,048) N = 3,784 cases	Annual avg at geocoded residential address, spatiotemporal models C-V R2 = 0.77 (post-1999) and R^2 = 0.69 (pre-1999)	Mean NHS: 18.3 (SD: 3.1) Mean HPFS: 17.5 (SD 2.7) IQR: 4	DM self-reported doctor diagnosed with confirmation of a subset of cases by medical record review: elevated plasma glucose or ≥1 DM symptoms (e.g., weight loss, thirst, polyuria) or use of hypoglycemic medication	Correlation (*r*): NR Copollutant models: $PM_{10-2.5}$
†Coogan et al. (2016) Longitudinal cohort 56 Metro areas, U.S. $PM_{2.5}$: 1999–2008 Outcome: 1995–2011	BWHS N = 33,771	Overall mean (1999–2008), LUR and BME hybrid model, C-V R^2 = 0.79	Mean: 13.9 (SD: 2.3) Range: 3.1–24.2 IQR: 2.9	Self-reported doctor diagnosed T2DM at age ≥30. Confirmation of 96% of cases in validation study using medical records.	Correlation (*r*): NR copollutant model: NR
†Coogan et al. (2012) Los Angeles, CA Longitudinal cohort $PM_{2.5}$: 2,000 Outcome: 1995–2005	BWHS N = 183 cases N = 3,992 black women (age 21–69 at baseline)	Annual avg, at residential zip code, kriging interpolation (10 × 10 km)	Mean 20.7 IQR: 20.3–21.6	Self-reported doctor diagnosed Type 2 diabetes mellitus at age ≥30	Copollutant model: NO_X

Table 7-9 (Continued): Epidemiologic studies of long-term exposure to $PM_{2.5}$ and diabetes.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Chen et al. (2013) Ontario, Canada Longitudinal cohort $PM_{2.5}$: 2001–2006 Outcome: 1996/2005–2010	Ontario, Diabetes Database n = 62,012 n = 6,310 cases	6 yr avg, at postal code, satellite derived AOD (10 × 10 km) Correlation between long-term avg from monitors and satellite based estimate, r = 0.77	Mean 10.6 (range: 2.6–19.1)	Incident diabetes administrative database (ICD9: 250 or ICD10: E10-E14)	Correlations (r): NR copollutant model: NR
†Hansen et al. (2016) Longitudinal cohort $PM_{2.5}$: 1990–2013 Outcome: 1993/99–2013	Danish Nurse Cohort n = 28,731 controls n = 1,137 cases	5 yr average at residence since 1990, 5 yr running average calculated from annual dispersion model [see Jensen et al. (2001)]. Model fit for PM NR.	Mean 18.1 (SD: 2.8)	National Diabetes Register of cases: hospital discharge (ICD-10:E10-14, DH36.0, DO24), chiropody as a diabetic patient, 5 blood-glucose measures within 1 year, or two blood glucose measures per year in 5 years, 2nd purchase of insulin or oral antidiabetic drugs within 6 mo. Note: T2D and T1D not distinguished	Correlations (r): NR copollutant models: NO_2
†Weinmayr et al. (2015) Longitudinal cohort Ruhr area, Germany $PM_{2.5}$: 2002–2003 Outcome: 2000/03–2005/08	HNR N = 3,607	Annual avg, dispersion model (1 × 1 km) Model fit for $PM_{2.5}$ NR (PM_{10} r > 0.80 for measured and modelled data)	Mean 16.8 (SD1.5)	Self-reported doctor diagnosed DM or use of diabetes medication or FBG ≥126 mg/dL at follow-up (random subset of respondents). Note: T2D and T1D not distinguished.	Correlations (r): NR copollutant model: NR

AOD = Aerosol Optical Density, avg = average, BME = Bayesian Maximum Entropy, BWHS = Black Women's Health Study, C-V = cross-validation, DM = diabetes mellitus, ICD = International Classification of Disease, HPFU = Health Professionals Follow-up Study, IGM = Impaired Glucose Metabolism; LUR = Land Use Regression; HNR = Heinz Nixdorf Recall study, MESA = Multiethnic Study of Atherosclerosis, NHS = Nurses' Health Study, NR = not reported; km = kilometer, T1D = Type 1 diabetes, T2D = Type 2 diabetes, yr = years.

†Studies published since the 2009 PM ISA.

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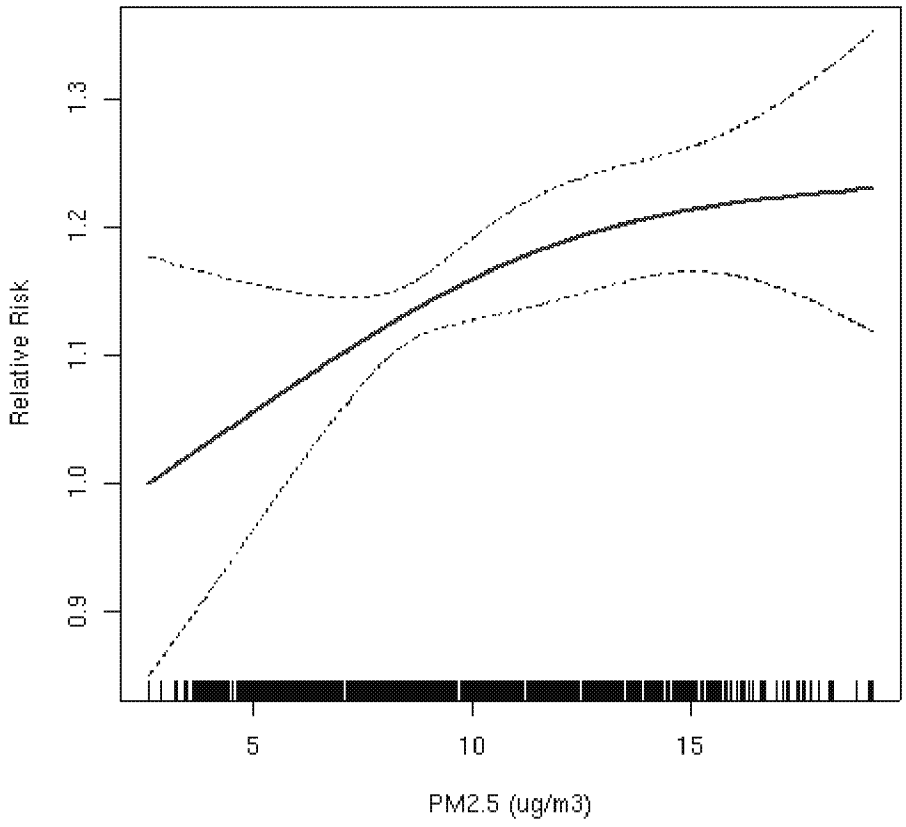
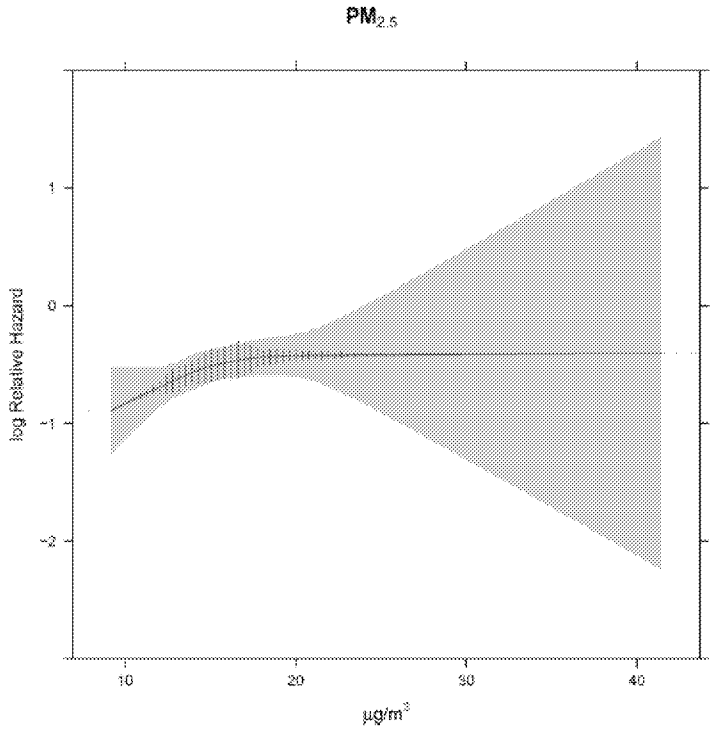
Several additional studies examining the effect of long-term $PM_{2.5}$ on the development of diabetes were conducted in Canada and Europe. Chen et al. (2013) combined several population-based surveys to establish a large cohort of men and women without diabetes living in Ontario, Canada (n = 62,012). This study found a positive association of long-term $PM_{2.5}$ exposures with incident diabetes [HR: 1.05 (95% CI: 1.01, 1.10)] after adjustment for covariates including individual and neighborhood indicators of SES and comorbidities. Chen et al. (2013) examined the shape of the concentration-response relationship using a natural cubic spline with two degrees of freedom and reported no statistical evidence of departure from linearity (Figure 7-8).



Source: Permission pending, Chen et al. (2013).

Figure 7-8 Concentration-response relationship between the concentration of $PM_{2.5}$ and incident diabetes among the cohort, depicted using a natural cubic spline function with two degrees of freedom. The hazard ratios were estimated by comparing to 2.6 µg/m^3.

In a study of Danish nurses, Hansen et al. (2016) reported relatively precise risk of diabetes in association with long-term exposure to $PM_{2.5}$ [HR: 1.18 (95% CI: 1.03, 1.38)]. In addition, the association with $PM_{2.5}$ persisted in the copollutant model adjusted for NO_2. An association of a similar magnitude but with a wider confidence interval was observed among participants in the HNR study [HR: 1.18 (95% CI: 0.78, 1.74)] (Weinmayr et al., 2015). Metrics derived to estimate $PM_{2.5}$ from traffic were also associated with incident diabetes in this study. The log relative hazard for the Danish Nurses Cohort is pictured in Figure 7-9 (Hansen et al., 2016). The curve is attenuated and the hazard estimate becomes less precise beginning above approximately 20 $\mu g/m^3$ but there was no statistical evidence of deviation from linearity.

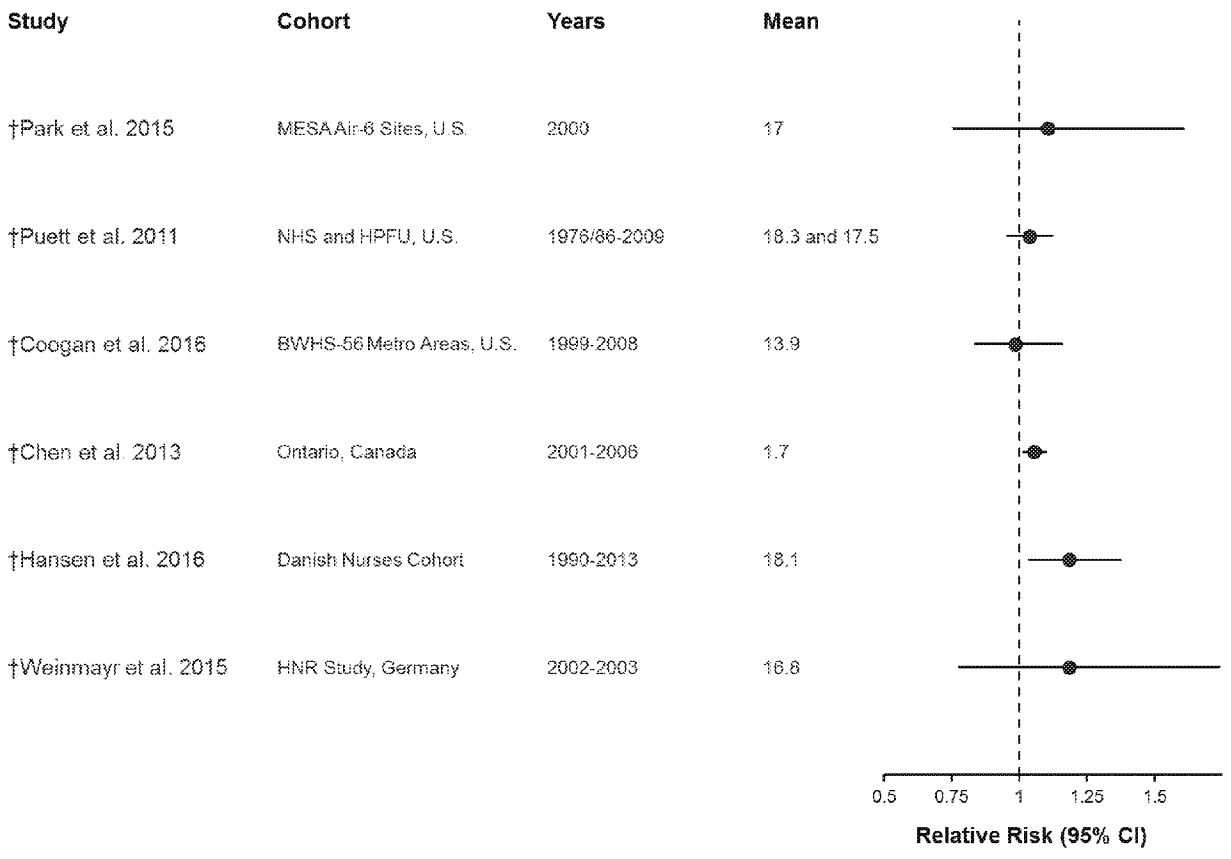


Source: Permission pending, Hansen et al. (2016).

Figure 7-9 Association (log relative hazard) between 5-year running average level at residence and incident diabetes in the Danish Nurses Study. Adjusted for age, calendar time, smoking, physical activity alcohol, fatty meat consumption, fruit and vegetable consumption, hypertension, myocardial infarction (MI), employment status, marital status and body mass index (BMI).

7.2.4.2 Summary

The risk of incident diabetes associated with long-term exposure $PM_{2.5}$ was increased in some, but not all, of the studies that were reviewed. With a few exceptions (Hansen et al., 2016; Chen et al., 2013), confidence intervals for the observed positive associations included the null. There were also differences regarding effect modification by sex (i.e., the effect size was larger in women enrolled in MESA but similar in women enrolled in NHS compared to men enrolled in HPFS). Note that Eze et al. (2015) reported a meta-analyzed pooled estimate for males [RR: 1.02 (95% CI: 0.96, 1.08)] and females [RR: 1.05 (95% CI: 1.01, 1.09)]. This pooled estimate, however, did not include the relatively recent MESA study or the extended analysis of the BWHS cohort, which reported no association. Based on a limited number of studies, associations with $PM_{2.5}$ were attenuated after adjustment for $PM_{10-2.5}$ with inconsistent findings in models adjusted NO_X or NO_2.



Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in $\mu g/m^3$. Relative risks are standardized to a 5 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations.

BWHS = Black Women's Health Study, CI = Confidence Interval, HPFU = Health Professionals Follow-up Study, HNR = Heinz Nixdorf Recall, MESA = Multi-Ethnic Study of Atherosclerosis, NHS = Nurses' Health Study.

†Studies published since the 2009 PM ISA.

Corresponding quantitative results are reported in Supplemental Table S7-1 (U.S. EPA, 2018).

Figure 7-10 Associations between long-term exposure to $PM_{2.5}$ and incident diabetes in longitudinal epidemiologic studies. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration.

7.2.5 Other Indicators of Metabolic Function

7.2.5.1 Inflammation

Experimental, epidemiologic, and controlled human exposure evidence link inflammation to the development of metabolic disease and comorbidities (Chapter 6 and Section 7.1.1 and Section 7.2.1).

Furthermore, it is widely believed that inflammation plays a critical role in the development of T2D and atherosclerosis, further complicating heart disease. Metabolic tissues, such as liver and adipose tissue, are essentially cocultures of metabolic (hepatocytes and adipocytes) and immune cells (i.e., Kupffer cells and macrophages) (Boron and Boulpaep, 2017). Furthermore, metabolic and immune responses (i.e., toll-like receptor and NFκβ) are coordinately regulated by inflammatory and endocrine signaling between organs and cells in response to environmental stimuli such as nutrients and pathogens. Therefore, the discussion below integrates inflammatory evidence from the cardiovascular, respiratory, and nervous system health effects chapters below with a specific focus on peripheral inflammation (Table 7-11).

Table 7-10 Study specific details from animal toxicology studies of inflammation and other indicators of metabolic function.

Study	Species, Sex, Strain, Sex, Diet, Age	Exposure Details (Pollutant, Concentration, Duration, Route)	Endpoints Evaluated
Haberzettl et al. (2016)	Mouse, male, C57BL/6J, ND or HFD, 8—12 weeks, n = 4–8	Columbus, OH CAPs, $PM_{2.5}$; 30–100 μg/m^3 Group 1: exposed for 6 h/day for 9 or 30 days. Group 2: treated with daily dose of water, metformin (50 mg/kg dose 2 days before, 100 mg/kg dose 1 day before and 300 mg/kg at the time of), or 1 mg/kg rosiglitazone 2 mg/kg two days before 9 days CAP exposure in drinking water.	Body weight, fasting blood glucose and insulin, HOMA-IR, organ weights, blood lipids, liver clinical chemistry, insulin signaling pathway, circulating bone marrow derived stem cells.
Kampfrath et al. (2011)	Mouse, male, C57BL/6, $NOx2^{-/-}$ (C57BL/6 background) Balb/c (TLR4wt), Tlr4Lps-d (TLRd, BALB/cAnPt background), c-fmsYFP (FVB/N background)	CAPs $PM_{2.5}$; 6 h/day, 5 days/week for: TLR4wt, TLRd, NOx2wt, and $NOx2^{-/-}$ for 20 weeks; c-fmsYFP for 23 weeks.	PM increases monocyte adherence and infiltration in cremaster muscle and mesenteric adipose tissue.
Liu et al. (2014c)	Mouse, male, C57BL/6 and $Ccr2^{-/-}$ (inflammation model), ND or HFD, 18 weeks, WT-FA (n = 8), WT-PM (n = 9), CCR2-FA (n = 9), CCR2-PM (n = 8)	Columbus, OH CAPs $PM_{2.5}$; 116.9 μg/m^3; 6 h/day, 5 days/week for 17 weeks, whole body inhalation	Body weight, glucose tolerance test, HOMA-IR, inflammation, liver and plasma lipids, vasorelaxation, macrophage infiltration, intra-vital leukocyte-endothelial interactions in adipose and muscle.

Table 7-11 (Continued): Study specific details from animal toxicology studies of inflammation underlying metabolic disease.

Study	Species, Sex, Strain, Sex, Diet, Age	Exposure Details (Pollutant, Concentration, Duration, Route)	Endpoints Evaluated
Liu et al. (2014a)	Mouse, male, KK-Ay, 5 weeks old, n = 7–8/group	Columbus, OH CAPs $PM_{2.5}$; 102.9 ± 19.16 µg/m^3, 6 h/day, 5 days/week, 5 weeks or 8 weeks December 28, 2011—February 28, 2012, OASIS exposure system	IPGTT or ITT, blood glucose, adiponectin, and leptin, bone marrow, spleen, epidydimal white adipose tissue, stromal vasculature cells were stained for inflammation (F4/80 + anti-CD11c + cells) and flow cytometry, aortic ring, O_2 consumption, CO_2 production, heat production, body weight, hepatic Akt, p38 and ERK phosphorylation
Liu et al. (2014b)	Mouse, KK-Ay (develop diabetes and overweightness), 5 or 7 weeks old, sex and genotype not reported, Exposure 1 (n = 7–8/group), Exposure 2 (n = 6/group), Exposure 3 (n = 8/group) IMD 0354 group n = 8, infliximab group n = 6	Columbus, OH CAPs $PM_{2.5}$ Exposure 1: 116.9 µg/m^3 for 6 h/day, 5 days/week, 5 weeks or 8 weeks Exposure 2: 139.5 µg/m^3 + infliximab (TNFα antibody) or artificial CSF for 6 h/day, 5 days/week, 5 weeks Exposure 3: 73.6 µg/m^3 + IMD-0354 (IKKB inhibitor) or DMSO for 6 h/day, 5 days/week, 4 weeks	Exposure 1: fasting blood glucose, HOMA-IR, hypothalamus TNFα, IL-6 and IKKB mRNA levels, oxidized PAPC Exposure 2: hypothalamic TNFα antagonism did not alter GTT, ITT, thermogenesis, body weight Exposure 3: IKKB inhibition IKK-NFkB pathway upregulation normalized PM effects on GTT and ITT, circulating monocytes (p = 0.0616), and visceral adipose monocytes ($p < 0.05$) compared to PM controls Body weight, food intake, glucose tolerance test, insulin levels, HOMA-IR, oxygen consumption, heat production, inflammation, inhibition of the cerebroventricular NFκβ pathway, insulin signaling pathway
Mendez et al. (2013)	Mouse, male, C57BL/6, normal diet (ND), 6 weeks, n = 4/group	Columbus, OH CAPs, $PM_{2.5}$; 94.4 µg/m^3; 6 h/day, 5 days/week for 10 mo, whole body inhalation	Inflammation, adipocyte size, ER stress markers
Wei et al. (2016)	Rat, pregnant females (12 weeks old) and male offspring, Sprague Dawley, ND or high fructose, gestation day 4—PND 3 or 8 weeks, filtered n = 8–10, unfiltered n = 6–10	Beijing, China air filtered for $PM_{2.5}$; 73.5 µg/m^3; continuous whole-body inhalation from gestation date 4 until PND 3 or 8 weeks	Body and organ weight, lung inflammation, LDL, TC, TG, malondialdehyde (MDA), GPL-1, chemoattractants, and anti-inflammatory cytokines

Table 7-11 (Continued): Study specific details from animal toxicology studies of inflammation underlying metabolic disease.

Study	Species, Sex, Strain, Sex, Diet, Age	Exposure Details (Pollutant, Concentration, Duration, Route)	Endpoints Evaluated
Xu et al. (2010)	Mouse, male, ND or high fat (HFD), wild-type or *p47*$^{phox-/-}$ ND, 3 weeks, n = 16/group	Columbus, OH CAPs, $PM_{2.5}$; diet study: 111.0 µg/m^3; 6 h/day, 5 days/week for 10 weeks, whole body inhalation	Glucose tolerance test, HOMA-IR, inflammatory markers and inflammation, adiposity, and vasomotor responses
Xu et al. (2011a)	Mouse, male, C57BL/6, ND, 4 weeks, n = 11 FA, n = 9 $PM_{2.5}$	Columbus, OH CAPs, $PM_{2.5}$; 94.4 µg/m^3; 6 h/day, 5 days/week for 10 mo, whole body inhalation	Body and adipose depot weights, glucose tolerance test, HOMA-IR, systemic inflammation, adipokines, mitochondrial size and number, gene expression, superoxide production/oxidative stress/Nrf2 signaling, insulin signaling pathway
Xu et al. (2011b)	Mouse, male, ApoE$^{-/-}$ (atherosclerosis), 4 weeks, n = 8/group	East Lansing, MI CAPs $PM_{2.5}$; 96.89 µg/m^3; 6 h/day, 5 days/week for 2 mo, whole body inhalation	Superoxide production, inflammatory response, WAT and BAT gene expression, mitochondrial number and size
Yan et al. (2014)	Rat, male, Sprague Dawley T1D (streptozotocin induced), 14 weeks, n = 8	Taipei Air Pollution Exposure System for Health Effects (TAPES) filtered for $PM_{2.5}$; 13.3 µg/m^3, 24 h/day, 7 days/week, for 16 weeks, whole body inhalation	Glucose/insulin/serum lipids, HOMA-IR, inflammatory and renal function blood biomarkers, urinary protein excretion, histopathology (heart, aorta, and kidney)
Zheng et al. (2013)	Mouse, male, C57BL/6, ND or high fat (HFD), 6 weeks, n = 4 FA, n = 5 CAPs exposed	Columbus, OH CAPs, $PM_{2.5}$; 74.6 µg/m^3; 6 h/day, 5 days/week for 3 or 10 weeks, whole body inhalation	Steatosis, steatohepatitis, glycogen storage, glucose tolerance test, fasting insulin and HOMA-IR, inflammatory pathway, liver and plasma lipids, gene expression, insulin signaling pathway
Zheng et al. (2015)	Mouse, male, C57BL/6, ND or high fat (HFD), 8 weeks; *p47*$^{phox-/-}$ (NADPH oxidase deficient, susceptible to infection and granulomatous inflammation), ND, 3 weeks, n = 8 per group	Columbus, OH CAPs, $PM_{2.5}$; 74.6 µg/m^3; 6 h/day, 5 days/week for 10 weeks, 111.0 µg/m^3; 6 h/day, 5 days/week for 9 mo, whole body inhalation	Liver steatosis, fibrosis and collagen production

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There is evidence for systemic inflammation following long-term exposure to $PM_{2.5}$ (also see Section 6.2.12). Studies with $ApoE^{-/-}$ mice that are prone to develop atherosclerosis demonstrated worsened inflammation in white adipose tissue accompanied by mitochondrial alterations and oxidative stress in brown adipose tissue (Xu et al., 2011b). Long term $PM_{2.5}$ exposure led to systemic increases in proinflammatory cytokines in experimental models and was also associated with blood biomarkers of inflammation such as CRP (Section 6.2.12). In experimental models, long term $PM_{2.5}$ CAPs exposures in wild type rodents fed a normal diet demonstrated increased blood TNF-α (<0.05) (Zheng et al., 2013; Xu et al., 2011b; Xu et al., 2011a; Xu et al., 2010), TGF-β1 ($p < 0.05$) (Zheng et al., 2015), monocyte counts (Kampfrath et al., 2011), CD4+ and CD8+ T lymphocytes (Deiuliis et al., 2012), IL-6 ($p < 0.01$) (Yan et al., 2014), and malondialdehyde ($p < 0.001$) (Wei et al., 2016).

Increases in blood inflammation markers and immune cells were consistent with the histological observation of liver and adipose inflammation. Specifically, nonalcoholic steatohepatitis and fibrosis were noted in $PM_{2.5}$ CAPs exposed mice (Zheng et al., 2015; Zheng et al., 2013) and increased monocyte/macrophage infiltration in visceral (Xu et al., 2010), epididymal (Mendez et al., 2013; Xu et al., 2011b) adipose tissue. Further molecular analysis demonstrated a clear and consistent decrease in Akt phosphorylation in liver, skeletal, adipose, and heart tissues (Liu et al., 2014c; Liu et al., 2014a; Zheng et al., 2013; Xu et al., 2011a) possibly mediated by activation of TLR/Iκκβ/JNK pathways leading to repression of the PI3K/Akt pathways (also discussed above in Section 7.2.3).

Genetic models highlight a critical role for innate immunity in metabolic disease outcomes. Specifically, long-term $PM_{2.5}$ exposure had reduced or no effect on hepatic inflammation, hepatic steatosis and fibrosis, and adipose inflammation in mice with a mutation in *p47phox* (a critical subunit of NADPH oxidase) or CC-chemokine receptor Type 2 (CCR2, a receptor for CCL2 chemokines). Furthermore, $PM_{2.5}$-mediated effects on insulin resistance (discussed above) were improved ($p < 0.05$) in these genetic mouse models (Zheng et al., 2015; Liu et al., 2014c; Xu et al., 2010). Similarly, $PM_{2.5}$ exposure and HFD feeding worsened hepatic fibrosis and reactive oxygen species generation, whereas these effects were rescued in a $p47^{phox-/-}$ mouse (nonfunctional NADPH oxidase activity) (Zheng et al., 2015). These results indicate that $PM_{2.5}$ impacts on inflammation and glucose levels are mediated by the innate immune system and potentially modified by dietary fat.

In a mouse model genetically predisposed to diabetes and obesity, long-term $PM_{2.5}$ exposure resulted in hyperglycemia ($p < 0.05$), insulin resistance ($p < 0.05$), and systemic inflammation (Liu et al., 2014a).

In summary, these phenotypic observations demonstrate that long-term $PM_{2.5}$ CAPs exposure in rodents causes increased incidence of peripheral and systemic inflammation, extending from the lung to peripheral vasculature and distal adipose and hepatic organs that are exacerbated by diet and genetic predisposition. The implication is that systemic inflammation may impact liver and adipose function, and consequently disrupt insulin signaling leading to a shift in glucose and lipid homeostasis (Section 7.2.3).

7.2.5.2 Liver Function

Hepatic steatosis in the absence of alcohol consumption (i.e., nonalcoholic fatty liver disease [NAFLD]) is a progressive chronic disease. The main pathological feature of NAFLD is excessive lipid accumulation (>5% and typically triglycerides) within the cytosol of hepatocytes. NAFLD is often asymptomatic, but if left untreated may progress to steatohepatitis (inflamed fatty liver) and progress to permanent liver injury including fibrosis and cirrhosis (Angrish et al., 2016a). NFALD is often associated with metabolic syndrome risk factors, including obesity, T2D, and cardiovascular disease, and is therefore considered the hepatic manifestation of metabolic syndrome.

7.2.5.2.1 Epidemiologic Studies

There were no studies of long-term exposure to $PM_{2.5}$ and liver function reviewed in the 2009 PM ISA. The evidence remains limited (Table 7-11) Li et al. (2016) conducted a study of participants in the Framingham Offspring and Third Generation cohorts to determine the association between long-term $PM_{2.5}$ exposure and hepatic steatosis. No associations with liver-to-phantom ratio (LPR) [$\beta = 0.00$ (95% CI: 0.00, 0.01)] or hepatic steatosis [OR: 0.86 (95% CI: 0.66, 1.19)] was observed. In a study in Augsburg, Germany, Markevych et al. (2013) reported increase in several liver enzymes that may indicate reduced liver function. In this study increases in gamma-glutamyltransferase (GGT) [9.21% (95% CI: 0.18, 18.77)] but not aspartate transaminase (AST) [1.26% (95% CI: −2.89, 5.42)] or alanine transaminase (ALT) [−1.81% (−7.94, 4.69)] were observed.

Table 7-11 Epidemiologic studies of long-term exposure to $PM_{2.5}$ and indicators of liver function.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†Li et al. (2016) Cross-sectional $PM_{2.5}$: 2003 Outcome: 2002–2005	Framingham Offspring and Third Generation Study N = 2,513	Annual avg (2003), spatio-temporal model, 1 × 1 km resolution, satellite derived AOD, out of sample R^2 = 0.88	Mean 10.6 (IQR: 1.4)	LPR Hepatic Steatosis	Correlations (*r*): NR Copollutant model: NR
†Markevych et al. (2013) Augsburg, Germany $PM_{2.5}$: 2008–2009 Outcome: 2004–2008	KORA N = 5,892 (31–85 yr)	ESCAPE Protocol	Mean: NR 5th–95th: 2.77	GGT AST ALT	Correlations (*r*): NR Copollutant model: NR

AOD = Aerosol Optical Depth, GGT = gamma-glutamyltransferase, AST = aspartate transaminase, ALT = alanine transaminase, LPR = Liver-to-Phantom Ratio, KORA = Cooperative Health Research in the Region of Augsburg.

†Studies published since the 2009 PM ISA.

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7.2.5.2.2 Toxicological Studies

There were no experimental studies of long-term exposure to $PM_{2.5}$ and liver function reviewed in the 2009 PM ISA. Several recent animal studies identified pathological fatty changes in the liver after exposure to $PM_{2.5}$ CAPs (Table 7-10). Specifically, histological phenotyping with H&E stain, Sirius-red, and Masson's trichrome staining identified hepatic steatosis, lobular and cellular inflammation, and perisinusoidal inflammation among mice exposed for 10 consecutive weeks to $PM_{2.5}$ CAPs (Zheng et al., 2013). Zheng also reported that $PM_{2.5}$ exposure reduced hepatic glycogen storage in the same animals. In a follow-up study Zheng et al. (2015) also found perisinusoidal fibrosis in mice exposed for 10 weeks or 9 months that was worsened by a high fat diet. However, there was no evidence of fibrosis in $p47^{phox-/-}$ mice (a mutation that inactivates NADPH oxidase (see Section 7.2.5.1) after 10 weeks of $PM_{2.5}$ CAPs exposure). Similarly, Liu et al. (2014c) identified steatosis marked by increased liver triglycerides ($p > 0.05$) and increased oil red O staining levels ($p > 0.05$) that were attenuated in $CCR2^{-/-}$ mice. Considered together, these results support that $PM_{2.5}$ exposure increases hepatic lipid levels and worsens progressive liver disease via innate immunity (see Section 7.2.5.1).

7.2.5.3 Endocrine Hormones

Body energy levels are maintained during feeding and fasting by many endocrine hormones secreted by organs and glands, e.g., the pancreas (insulin and glucagon), gastrointestinal tract (ghrelin), adipose tissue (adiponectin and leptin), neurons (i.e., epinephrine), and adrenal gland (glucocorticoids, i.e., cortisol). There are two recent studies reporting changes in adipose endocrine hormones. Xu et al. (2011a) identified decreased ($p < 0.05$) adiponectin and leptin blood levels in C57BL/6 mice exposed 6 hours/day, 5 days/week for 10 months compared to vehicle controls. Liu et al. (2014a) identified decreased plasma adiponectin and increased leptin levels ($p < 0.05$) in KK-Ay mice 5 weeks after $PM_{2.5}$ exposure compared to FA controls, whereas no differences were detected 8 weeks after exposure.

7.2.5.4 Adiposity and Weight Gain

Adiposity, particularly visceral adiposity, and weight gain are risk factors for metabolic syndrome, T2D and cardiovascular disease. Although most epidemiologic studies consider BMI as a potential confounder or modifier of the association between $PM_{2.5}$ and cardiovascular disease, there were no studies of the association of long-term exposure to $PM_{2.5}$ with adiposity or weight gain reviewed in the 2009 PM ISA.

7.2.5.4.1 Epidemiologic Studies

A limited number of epidemiologic studies of adiposity and weight gain (Table 7-12) are currently available for review. White et al. (2016) examined the associations of long-term exposure to $PM_{2.5}$ with weight gain among women in the BWHS. Overall, no evidence of an association between $PM_{2.5}$ was observed in this population.

Mao et al. (2017) reported increased risk of childhood overweight and obesity, comparing the highest to the lowest quartile of exposure, with exposure to $PM_{2.5}$ averaged over the first 2 years of life, as well as during each trimester of pregnancy. This study also indicated the highest risk among children of mothers who were overweight or obese prior to pregnancy and exposed to $PM_{2.5}$. There was a dose-response relationship between $PM_{2.5}$ and childhood obesity and overweight that was indicated after the median exposure (10.5−10.9 $\mu g/m^3$) for each of the exposure windows. Exposure during the second trimester showed a steeper C-R relationship.

Table 7-12 Epidemiologic studies of long-term exposure to $PM_{2.5}$, overweight and obesity.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†White et al. (2016) 56 Metro areas, U.S. Prospective cohort $PM_{2.5}$: 1998–2008 Outcome: 1995–2011	BWHS N = 38,374 Follow-up 16 yr	Multiyear avg, LUR with BME (C-V R^2 = 0.79) for residential histories	Mean: 13.9	Weight change	Correlations (*r*): NR Copollutant model: NR
†Mao et al. (2017) Boston, MA Prospective cohort 2003–2012	BMC N = 1,446 mother-infant pairs	Closest monitor, preconception, 1st, 2nd, 3rd, 2 first 2 yr of life	NR	Childhood overweight and obesity	Correlations (*r*): NR Copollutant model: NR

BME = Bayesian Maximum Entropy; BMC = Boston Medical Center; HOMA-IR = Homeostatic Model Assessment of Insulin; Resistance; LUR = Land Use Regression; NR = not reported.

†Studies published since the 2009 PM ISA.

7.2.5.4.2 Toxicological Studies

Long-term $PM_{2.5}$ exposures had little to no effect on animal body weight. Long-term $PM_{2.5}$ exposure affected abdominal fat mass (measured by MRI) in one study ($p < 0.05$), although there was no interaction between high fat feeding and $PM_{2.5}$ on abdominal fat mass (Xu et al., 2010). Liu et al. (2014a) identified a trend ($p = 0.0578$) toward increased epididymal white adipose tissue 5 weeks after exposure, but found no difference between $PM_{2.5}$ and filtered air 8 weeks after exposure. Studies are detailed in Table 7-10.

7.2.5.5 Blood Lipids

7.2.5.5.1 Epidemiologic Studies

The previous PM ISA did not include any relevant epidemiologic studies describing associations between long-term exposure to $PM_{2.5}$ and blood lipid levels. The available literature includes ecological studies or studies conducted at relatively high concentration (>20) (Calderón-Garcidueñas et al., 2013; Chuang et al., 2011). In addition, Wallwork et al. (2017) examined blood lipids in the context of all the components of metabolic syndrome and observed increased triglycerides among older adult males in the NAS in association with annual average $PM_{2.5}$ concentration. Yitshak Sade et al. (2016) examined blood lipids, in addition to HbA1c and FBG, and reported associations of 3-month average $PM_{2.5}$ exposure with HDL and LDL in a retrospective study in Israel noting larger effect sizes among those with diabetes.

7.2.5.5.2 Toxicological Studies

In mice, long-term $PM_{2.5}$ CAPs exposures resulted in increased ($p < 0.05$) liver (Liu et al., 2014c), (116 $\mu g/m^3$ for 17 weeks), and blood (Zheng et al., 2013), (74 $\mu g/m^3$ for 9 months), triglycerides and blood cholesterol (Zheng et al., 2013) levels. It is important to note, however that rodent cholesterol dietary intake and plasma clearance is markedly higher than humans meaning that rodents, on average, have much lower plasma LDL levels (7 mg/dl) than humans (120 mg/dl). Study characteristics are detailed in Table 7-10.

7.2.5.6 Blood Pressure and Hypertension

Small increases in SBP, PP, and MAP were found in association with $PM_{2.5}$ in MESA and Sister Study but not in all the available studies (Section 6.3.7). A limited number of animal toxicological studies

demonstrate a relationship between long-term exposure to $PM_{2.5}$ and consistent increases in BP (Section 6.2.7.2). These results are in coherence with epidemiologic studies reporting positive associations between long-term exposure to $PM_{2.5}$ and hypertension (Section 6.2.18).

7.2.6 Gestational Diabetes

Several studies of gestational diabetes were conducted. Generally, the results of the studies were inconsistent, though several reported positive associations with gestational diabetes or impaired glucose tolerance with $PM_{2.5}$ exposures during the second trimester. While the evidence base for gestational diabetes is growing, it is still limited to a relatively small number of studies which report generally inconsistent results (see Section 9.2.1 on Reproductive and Developmental Effects for more details).

7.2.7 Type 1 Diabetes

Type 1 diabetes (T1D) mellitus, which typically affects children and young adults, is a chronic condition that results when the pancreas fails to produce the insulin needed for glucose homeostasis. There were no studies of T1D reviewed in the 2009 PM ISA.

7.2.7.1 Epidemiologic Studies

The evidence relating to the effect of long-term exposure to $PM_{2.5}$ on T1D is limited to a study examining the age of onset as opposed to development of the disease (Table 7-12). Beyerlein et al. (2015) analyzed data from the Bavaria, Germany registry of incident diabetes in children. $PM_{2.5}$ was associated with reduced age of onset of diabetes [10th percentile age of diagnosis −1.4 years (95% CI: −1.97, 0.77) per 2 SD increase] after adjustment for level of urbanization. Manifestation of T1D was not associated with PM_{10} in a larger study designed to replicate these findings (Rosenbauer et al., 2016). Ambient pollution concentrations were modelled at a lower spatial resolution in the Rosenbauer et al. (2016) study. In addition, Beyerlein et al. (2015) adjusted for individual-level SES (i.e., parental education) while Rosenbauer et al. (2016) adjusted for community-level SES (i.e., German Index of Multiple Deprivation).

Table 7-13 Epidemiologic studies of long-term exposure to $PM_{2.5}$ and age of onset for Type 1 diabetes.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Beyerlein et al. (2015) Cross-sectional Bavaria, Germany 2009–2013	Registry mean age = 9.3 yr N = 617	Annual avg (2001) Kriging interpolation and LUR (1 × 1 km grid), at residential address	NR	Age of onset T1D (islet antibody test)	Correlations (*r*): NR Copollutant models; NR
†Rosenbauer et al. (2016) Westphalia, Germany 2001–2006 PM_{10}: 2006–2014	Registry N = 6,807 (0–19)	REM-CALGRID model (8 × 8 km grid), at residential zip code	NR	Age of onset T1D	Correlations (*r*): NR Copollutant models; NR

Avg = average; km = kilometer; LUR = land use regression; N, n = sample size; NR = Not reported; REM-CALGRID = Regional Eulerian Model—California Grid Model; T1D = Type 1 Diabetes, yr = years.

†Studies published since the 2009 PM ISA.

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7.2.7.2 Toxicological Studies

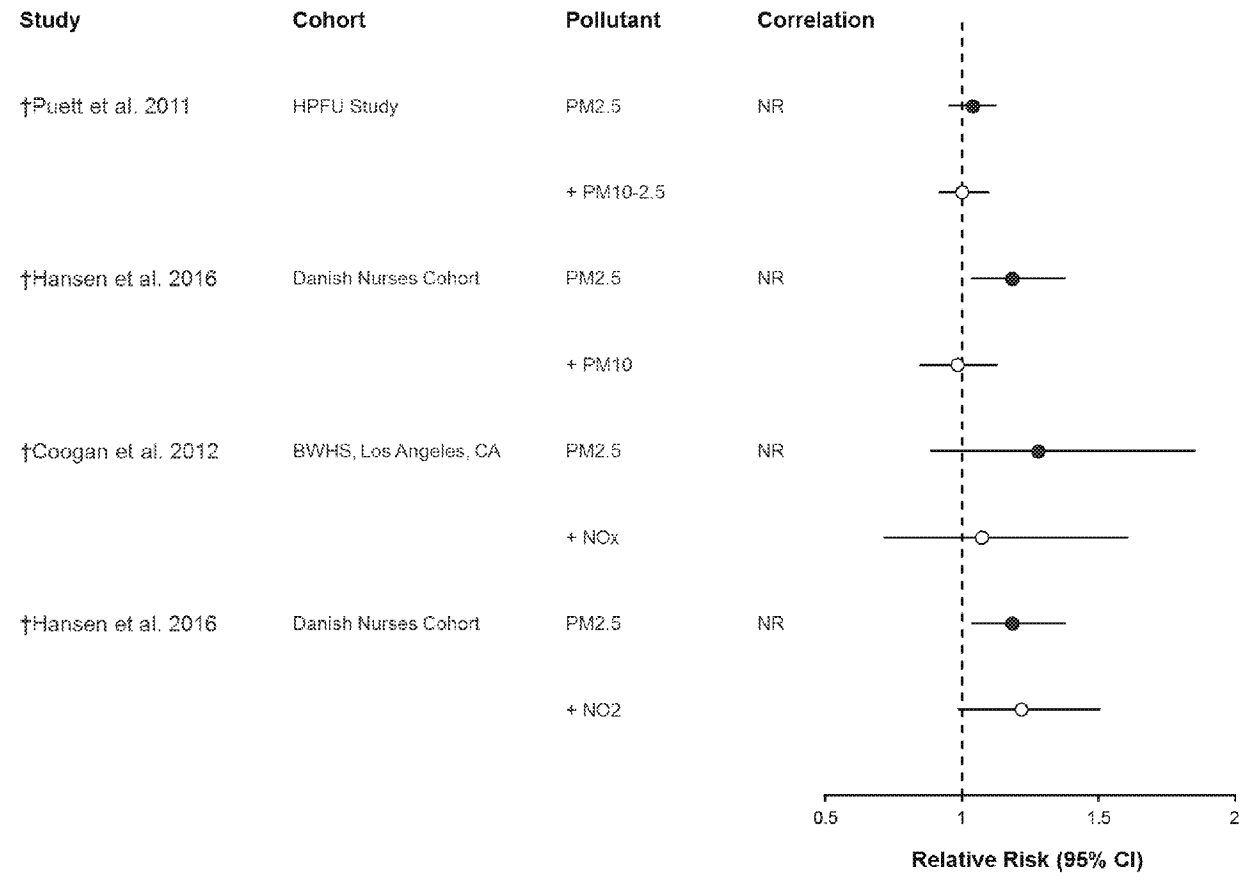
In a Type 1 diabetic rat model, $PM_{2.5}$ exposure had no effect on glucose homeostasis, insulin sensitivity, or blood lipid chemistry, however glycated hemoglobin (HbA1c, a marker of elevated glucose) was increased ($p < 0.05$) (Yan et al., 2014).

7.2.8 Associations between $PM_{2.5}$ Components and Sources and Metabolic Effects

There were no studies of the association of long-term $PM_{2.5}$ components or sources with metabolic effects reviewed in the 2009 PM ISA. The literature on this topic remains limited. Weinmayr et al. (2015) developed metrics to distinguish exposure to total $PM_{2.5}$ from $PM_{2.5}$ from traffic using data from the HNR Study in Germany. In this longitudinal analysis of T2D (mean follow-up 5.1 years), the authors reported similar hazards when standardized to an IQR increase [HR: 1.08 (95% CI: 0.89, 1.29) total $PM_{2.5}$ vs. HR: 1.1 (95% CI: 0.99, 1.23) traffic $PM_{2.5}$].

7.2.9 Copollutant Confounding

A limited number of studies are available that report results from copollutant models. Overall, estimates were not robust to adjustment for NO_2, NO_X or $PM_{10-2.5}$. Puett et al. (2011) reported that the weak association of long-term exposure to $PM_{2.5}$ with incident diabetes [HR: 1.04 (95% CI: 0.95, 1.13)] was null after adjustment for $PM_{10-2.5}$ [HR: 1.00 (95% CI: 0.91, 1.11)]. Note that the results for Coogan et al. (2012) included in the figure are for an interim analysis of women from Los Angeles, CA not the full cohort. No association between $PM_{2.5}$ and diabetes was observed in the later analysis of the entire cohort that included additional years of follow-up. The larger HR reported by Hansen et al. (2016) of 1.18 (95% CI: 1.03,1.38) among Danish nurses was null after adjustment for PM_{10} [HR: 0.98 (95% CI: 0.84, 1.13)] but persisted after adjustment for NO_2 [HR: 1.22 (95% CI: 0.98, 1.51)]. The decrease in HOMA-IR reported by Thiering et al. (2016) among children was also diminished after adjustment for NO_2 in a copollutant model (not presented in Figure 7-11). In this study, the 14.6% (95% CI −2.5, 34.6) increase in HOMA-IR was reduced 4.3% (95% CI: −14.8, 27.5) in the copollutant model.



Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in $\mu g/m^3$. Hazard Ratios are standardized to a 5 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations.

BWHS = Black Women's Health Study, CI = Confidence Interval, HPFU = Health Professionals Follow-up Study, NO_2 = nitrogen dioxide, NO_X = Oxides of Nitrogen, NR = Not Reported.

†Studies published since the 2009 PM ISA.

Corresponding quantitative results are reported in Supplemental Table S7-2 (U.S. EPA, 2018).

Figure 7-11 Copollutant model results for studies of long-term exposure to $PM_{2.5}$ and incident diabetes. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration.

7.2.10 Metabolic Disease Mortality

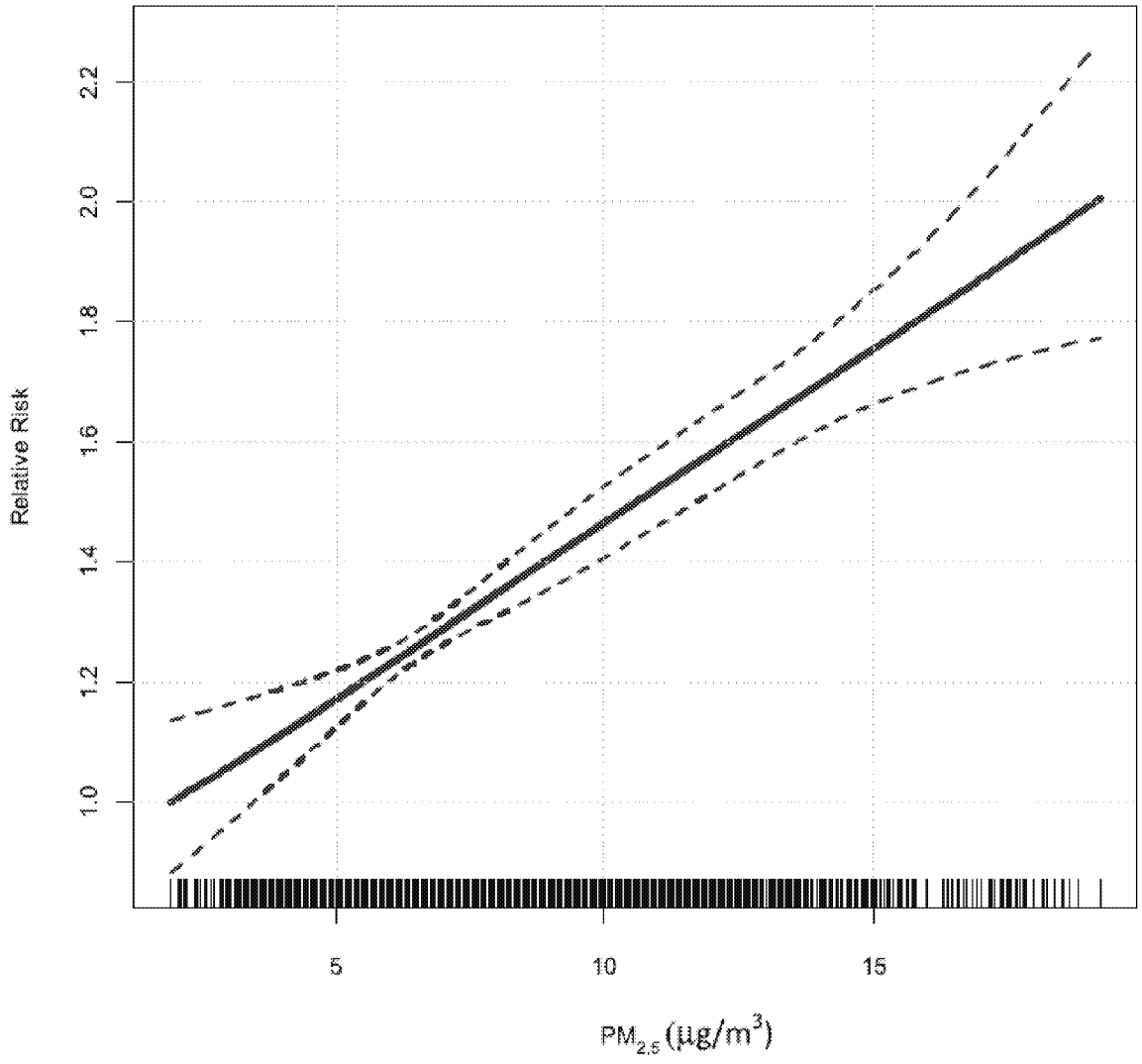
Studies that examine the association between long-term $PM_{2.5}$ exposure and cause-specific mortality outcomes, such as diabetes or other metabolic disease mortality, provide additional evidence for $PM_{2.5}$-related metabolic effects, specifically whether there is evidence of an overall continuum of effects. Evidence from studies of long-term $PM_{2.5}$ exposure and mortality are presented in detail in Section 11.2; no studies investigating metabolic disease mortality related to long-term $PM_{2.5}$ exposure were identified in

the 2009 PM ISA (U.S. EPA, 2009). Recent analyses from two well-established cohorts (the ACS and CanCHEC cohorts) have included this outcome and are summarized here to inform the effect of long-term $PM_{2.5}$ exposure on metabolic disease effects (Figure 7-12).

Pope et al. (2014), Turner et al. (2016) and Jerrett et al. (2016) all used the extended follow-up period of the ACS (1982–2004) to examine the associations between long-term $PM_{2.5}$ exposure and mortality due to diabetes. Pope et al. (2014) and Turner et al. (2016) assigned exposure using an LUR-BME model and observed positive associations with deaths due to diabetes. Jerrett et al. (2016) assigned $PM_{2.5}$ exposure using six different methods and observed positive associations with diabetes mortality for each one, though the precision of the association varied across exposure assessment methods. The most precise estimate was observed for the monitor-LUR hybrid model (HR: 1.09; 95% CI: 1.03, 1.17), and was similar in magnitude to the associations observed by Pope et al. (2014) and Turner et al. (2016).

A recent series of studies conducted in Canada linked census data with data from the Canadian Mortality Database to create the Canadian Census Health Environment Cohort (CanCHEC) and evaluated the relationship between long-term $PM_{2.5}$ exposure and metabolic disease mortality. These studies either examined deaths due to diabetes or the combination of circulatory disease and diabetes in their evaluation of metabolic disease. The authors observed positive associations between diabetes mortality and long-term $PM_{2.5}$ exposure, with similar estimates for satellite-derived estimates and ground monitor estimates (Crouse et al., 2016; Crouse et al., 2015; Brook et al., 2013a). The hazard ratios remained positive, but were less consistent in magnitude for circulatory disease and diabetes deaths combined (Weichenthal et al., 2016; Crouse et al., 2015). Pinault et al. (2016) linked a subset of participants from the CanCHEC cohort to the Canadian Community Health Survey, which allowed them to include an expanded set of individual-level covariates in their analyses. Among the nearly 300,000 participants included in the study, the authors observed positive associations with combined circulatory and diabetes mortality similar in magnitude to those observed for diabetes mortality in the larger cohort (Crouse et al., 2016; Crouse et al., 2015).

An important consideration in characterizing the association between long-term $PM_{2.5}$ exposure and mortality is whether the concentration-response relationship is linear across the full concentration range that is encountered, or if there are concentration ranges where there are departures from linearity. Brook et al. (2013a) conducted an analysis of the CanCHEC cohort to inform the shape of the C-R relationship for the association between long-term exposure to $PM_{2.5}$ and diabetes mortality, observing a linear, no-threshold relationship across the full range of concentrations measured during the study (Figure 7-12). C-R relationships for metabolic morbidity outcomes are described in Supplemental Table S7-4 (U.S. EPA, 2018).



Note: The association shown represents the results from the standard Cox survival model with a natural spline of $PM_{2.5}$ with two degrees of freedom. Tick marks on the *x*-axis represent the position of $PM_{2.5}$ concentration measured in µg/m^3. Dashed lines represent 95%confidence intervals (CIs).

Source: Permission pending, Brook et al. (2013a).

Figure 7-12 The relative risk of diabetes-related mortality in relation to long-term $PM_{2.5}$ exposure.

7.2.11 Summary and Causality Determination

There were no causal conclusions for metabolic effects in the 2009 PM ISA (U.S. EPA, 2009). The literature pertaining to the effect of long-term exposure to $PM_{2.5}$ and metabolic effects has expanded substantially since the 2009 PM ISA, with multiple epidemiologic and experimental studies currently available for review. Positive associations between long-term exposure to $PM_{2.5}$ and diabetes-related mortality were observed in well-established cohorts in the U.S. and Canada. The mortality findings are supported by epidemiologic and experimental studies reporting effects on glucose and insulin homeostasis, as well as other indicators of metabolic function (e.g., peripheral inflammation and liver function). Findings from epidemiologic studies of metabolic disease were not entirely consistent and consideration of copollutant confounding was limited; however, some well-conducted studies reported positive associations of long-term exposure to $PM_{2.5}$ with metabolic syndrome and its components (e.g., increased blood glucose, insulin resistance, and dyslipidemia) and the incidence of diabetes. The evidence characterizing the relationship between long-term exposure to $PM_{2.5}$ and metabolic effects is detailed below (Table 7-14), using the framework for causal determination described in the Preamble to the ISAs (U.S. EPA, 2015).

Several recent epidemiologic analyses of the ACS cohort found positive associations between long-term $PM_{2.5}$ exposure, which was estimated using a variety of exposure assessment methods, and mortality due to diabetes (Jerrett et al., 2016; Turner et al., 2016; Pope et al., 2014). Positive associations were also identified between long-term $PM_{2.5}$ exposure and diabetes in series of analyses from the large Canadian cohort, CanCHEC (Crouse et al., 2016; Crouse et al., 2015; Brook et al., 2013a). When the CanCHEC cohort was combined with Canadian Community Health Survey Pinault et al. (2016) observed positive associations with combined circulatory disease and diabetes mortality. Additionally, Brook et al. (2013a) observed a linear, no-threshold relationship across the full range of concentrations measured in this cohort.

Well-conducted studies from Canada and Denmark reported positive associations between long-term $PM_{2.5}$ exposure and the incidence of T2D (Hansen et al., 2016; Chen et al., 2013). A relationship between long-term $PM_{2.5}$ exposure and incident diabetes was not supported by analyses of data from well-established U.S. cohorts including MESA, NHS, HPFU, and BWHS, however (Coogan et al., 2016; Park et al., 2015; Puett et al., 2011). A longitudinal analysis of older adult male participants in the NAS (Wallwork et al., 2017), reported associations of long-term $PM_{2.5}$ with metabolic syndrome and several components including increased FBG and dyslipidemia. Another longitudinal epidemiologic study provided additional support, reporting an increase in blood glucose level in association with 28-day average $PM_{2.5}$ exposure (Lucht et al., 2018a). Several cross-sectional analyses also showed associations with measures of glucose and insulin homeostasis (Section 7.2.3.1). The limited number of epidemiologic studies that considered confounding by copollutants did not consistently report that the effect of $PM_{2.5}$ remained after adjustment for NO_2, NO_X or PM_{10}.

Experimental animal studies address some of the uncertainty in the epidemiologic evidence related to the independent effect of $PM_{2.5}$ exposure by providing evidence of direct effects on metabolic function. The animal toxicological studies provided evidence that long-term $PM_{2.5}$ exposure resulted in impaired insulin signaling, glucose tolerance, and insulin resistance (Section 7.2.3). In addition, these pathophysiological changes were often accompanied by increased inflammatory markers in the blood and peripheral inflammation in adipose, liver and heart tissues (Section 7.2.5). Most of the animal toxicology studies evaluating effects on glucose and insulin derived $PM_{2.5}$ CAPs from the same Columbus, OH air shed and were performed by the same group of investigators. Importantly, long-term $PM_{2.5}$ exposure effects were evaluated in animals fed a normal diet and animals models of metabolic syndrome-like phenotypes and provided evidence that long-term $PM_{2.5}$ exposure could lead to development or worsening of metabolic syndrome or its risk factors.

Epidemiologic studies report positive associations between long-term $PM_{2.5}$ exposure and diabetes-related mortality. Although results were not consistent across cohorts, some epidemiologic studies report positive associations with incident diabetes, metabolic syndrome, glucose and insulin homeostasis. Consideration of copollutant confounding was limited. Some support was provided by experimental studies demonstrating increased blood glucose, insulin resistance, and inflammation and visceral adiposity but the experimental evidence was not entirely consistent. **Overall, the collective evidence is suggestive of, but is not sufficient to infer, a causal relationship between long-term $PM_{2.5}$ exposure and metabolic effects.**

Table 7-14 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between long-term $PM_{2.5}$ exposure and metabolic effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Mortality			
Consistent findings in epidemiologic studies of diabetes-related mortality at relevant concentrations.	Epidemiologic studies in well-established U.S. and Canadian cohorts (ACS and CanCHEC) reported positive associations with deaths due to diabetes.	Section 7.2.10	Mean concentrations across studies: 6.3–12.6 $\mu g/m^3$

Table 7-14 (Continued): Summary of evidence indicating that the evidence is suggestive, but not sufficient to infer a causal relationship between long-term $PM_{2.5}$ exposure and metabolic effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Type 2 Diabetes			
Inconsistent findings from multiple epidemiologic studies of incidence of T2D; however, some high quality epidemiologic studies support a positive association.	Longitudinal studies conducted in Canada and in Denmark report positive associations. Prospective cohort studies (MESA, NHS and HPFU, BWHS) conducted in the U.S. reported null associations with T2D or associations with wide CIs.	Hansen et al. (2016) Chen et al. (2013)	Means 10.6–18.1 µg/m^3 Mean concentrations across studies 13.9–18.3 µg/m^3
Consistent associations in epidemiologic studies with metabolic syndrome and its components	Longitudinal analyses metabolic syndrome and its components. Support from cross-sectional analysis reporting positive associations with measure of glucose and insulin homeostasis.	Wallwork et al. (2017) Lucht et al. (2018a) Section 7.2.2 Section 7.2.3	Mean 10.5 Mean concentrations of cross-sectional studies 13.5–72.6 µg/m^3
Limited evidence from copollutant models in epidemiologic studies	Most studies do not consider potential confounding by copollutants in the analysis; the small number of studies that present copollutant models are inconsistent.	Section 7.2.9	
Uncertainty regarding exposure measurement error	Evidence base too limited to evaluate consistence within and across exposure assessment methods.		
Toxicological studies provide coherence for associations with metabolic syndrome and its components observed in the epidemiologic studies	Strong evidence for impaired insulin signaling, insulin resistance, increased blood glucose, systemic inflammation, and peripheral inflammation. Toxicological evidence demonstrating effects on insulin resistance is limited because multiple studies are from same air shed (Columbus, OH air shed). Finding of increased BP from a limited number of toxicological studies provide coherence for effects on metabolism.	Section 7.2.3.2,Section 7.2.5	513.3–139.5 µg/m^3 $PM_{2.5}$ CAPs exposure for 4–16 weeks

Table 7-14 (Continued): Summary of evidence indicating that the evidence is suggestive, but not sufficient to infer a causal relationship between long-term $PM_{2.5}$ exposure and metabolic effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Gestational Diabetes			
Findings from a limited number of epidemiologic studies were not consistent; support from other lines of evidence is lacking.	Although findings not entirely consistent, some studies reported associations with gestational diabetes or IGT with $PM_{2.5}$ exposures in the 2nd trimester.	Section 9.2.1	Mean concentrations across studies 9.7–11.9 $\mu g/m^3$
Other Indicators of Metabolic Function			
Biological plausibility derived from multiple lines of evidence	Multiple high quality epidemiologic studies finding positive associations between long-term $PM_{2.5}$ exposure and metabolic disease mortality, cardiovascular disease, diabetes, insulin resistance. Toxicological evidence provide coherence for potential pathways connecting $PM_{2.5}$ exposure to metabolic syndrome components, diabetes, and cardiovascular disease.	Section 7.2.1 Figure 7-2 Section 7.2.3, Section 7.2.4 and Section 7.2.10 Chapter 6	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

†Studies published since the 2009 PM ISA.

7.3 Short-term $PM_{10-2.5}$ Exposure and Metabolic Effects

There were no epidemiologic or experimental studies of short-term exposure to $PM_{10-2.5}$ and metabolic effects such as diabetes or glucose and insulin homeostasis reviewed in the 2009 PM ISA nor have recent studies become available. **The evidence is inadequate to infer the presence or absence of a causal relationship between short-term $PM_{10-2.5}$ exposure and metabolic effects.**

7.4 Long-Term $PM_{10-2.5}$ Exposure and Metabolic Effects

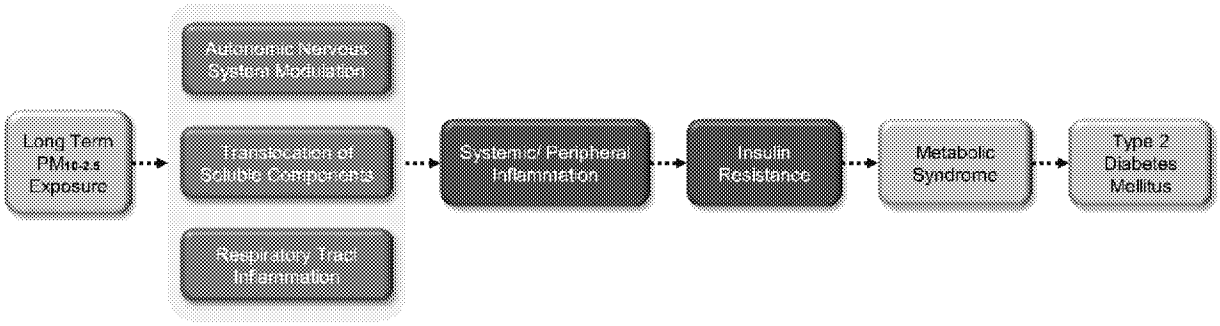
There were no studies of $PM_{10-2.5}$ and metabolic effects reviewed in the 2009 PM ISA. The discussion of the limited number of recent studies long-term $PM_{2.5}$ exposure and metabolic effects opens with a discussion of biological plausibility (Section 8.1.1) that provides background for the subsequent section in which the evidence related to T2D is presented. The collective body of evidence is integrated across and within scientific disciplines[70], and the rationale for the causality determination is outlined in Section 7.4.3.

7.4.1 Biological Plausibility

This section describes biological pathways that potentially underlie metabolic effects resulting from long-term exposure to $PM_{10-2.5}$. Figure 7-13 graphically depicts the potential pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" exposure to $PM_{10-2.5}$ may lead to metabolic health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 7.4.

Soluble components of $PM_{10-2.5}$ may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. The extent to which translocation into the systemic circulation occurs is currently uncertain (Chapter 4). Furthermore, the PM administered dose depends on deposition, which is a function of particle size, intake, and physical chemistry as well as modifying factors such as lifestages and species. It is possible that deposition of $PM_{10-2.5}$ may initiate pathways that include ANS modulation, translocation of soluble components, and respiratory tract inflammation that converge upon inflammation leading to insulin resistance. Therefore, implicit relationships between long-term $PM_{10-2.5}$ exposure and observed health effects that include diabetes can be drawn even though the evidence is limited. For example, Wolf et al. (2016) reported positive increases in CRP (a nonspecific marker of inflammation produced by the liver) supporting a pathway toward systemic and peripheral inflammation. Wolf et al. (2016) also reported a positive association with HOMA-IR, a measure of insulin resistance. These events and endpoints are on the pathway leading to T2D, an outcome that was positively associated with long-term exposure to $PM_{10-2.5}$ by Puett et al. (2011).

[70] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{10-2.5}$ concentrations unless otherwise noted.



The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 7-13 Potential biological pathways for metabolic effects following long-term $PM_{10-2.5}$ exposure.

As described here, there are proposed pathways by which long-term exposure to $PM_{10-2.5}$ could lead to metabolic health effects. One pathway involves ANS modulation, translocation of soluble components, and respiratory tract inflammation that may lead to systemic and peripheral inflammation that is linked to insulin resistance and metabolic syndrome comorbidities. Together, these proposed pathways provide limited biological plausibility for epidemiologic results of metabolic health effects, highlight areas where further scientific understanding is needed, and will be used to support a causal determination, which is discussed later in the chapter (Section 7.4.3).

7.4.2 Type 2 Diabetes

Puett et al. (2011) observed a small increased hazard in association with long-term exposure to $PM_{10-2.5}$ [HR: 1.05 (95% CI: 0.98,1.13)] that remained after adjustment for $PM_{2.5}$ in the NHS. Cross-sectional studies provided supporting evidence that long-term $PM_{10-2.5}$ exposure is associated with IGM, diabetes, HOMA-IR, leptin and CRP (Wolf et al., 2016; Teichert et al., 2013). Overall, the number of epidemiologic studies (Table 7-14) is limited but findings are compatible with an effect of $PM_{10-2.5}$.

Table 7-15 Summary of studies examining the relationships for long-term exposure to $PM_{10-2.5}$ and diabetes.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Puett et al. (2011) Longitudinal cohort U.S. $PM_{10-2.5}$: 12 mo prior to diagnosis Outcome NHS: 1976–2009 Outcome HPFS: 1986–2009	NHS (N = 74,412) and HPFS (N = 15,048) N = 3,784 cases	Annual avg at geocoded residential address, spatiotemporal models C-V $PM_{2.5}$, R^2 = 0.77 (post-1999) and R^2 = 0.69 (pre-1999) C-V PM10 R^2 = 0.62 (Difference method)	Mean NHS: 18.3 (SD: 3.1) Mean HPFS: 17.5 (SD 2.7) IQR: 4	Incident diabetes (self-reported doctor diagnosed and confirmation by medical record review)	Correlations (*r*): NR Copollutant models Positive with $PM_{2.5}$
†Teichert et al. (2013) Cross-sectional Ruhr area, Germany PM_{10} and $PM_{2.5}$: 2008–2009 Outcome: 2008–2009	SALIA n = 363 (random sample of women 54–55)	LUR, back extrapolation to baseline examination (1984) to assign exposure at residence (difference method)	Mean 18.0 (1.4) Back extrapolated concentration: Mean 34.0 (3.2)	IGM = ≥100 mg/dl or previous diagnosis of diabetes	Correlations (*r*): NR Copollutant models: NR
†Wolf et al. (2016) Augsburg and two adjacent rural counties, Germany Cross-sectional $PM_{10-2.5}$: 2008–2009	KORA N = 2,944 Mean age: 56.2 yr	Annual avg, LUR, at residence (ESCAPE protocol)	Mean (SD) 6.2–6.3 (1.1)	HOMA-IR, Glucose, Insulin, HbA1c, Leptin, hs-CRP	Correlations (*r*): $PM_{2.5}$ *r* = 0.32, NO_2 *r* = 0.79 Copollutant models: NR

Avg = average, ESCAPE = European Study of Cohorts for Air Pollution Exposure, HbA1c = glycated hemoglobin, HOMA-IR = homeostatic model assessment of insulin resistance, HPFU = Health Professionals Follow-up Study, IGM = Impaired Glucose Metabolism, KORA = Cooperative health research in the Region of Augsburg, LUR = land use regression, N, n = number of subjects, NHS = Nurses' Health Study; SALIA = Study on the influence of air pollution on lung function, inflammation and aging, yr = years.

†Studies published since the 2009 Integrated PM ISA.

7.4.3 Summary and Causal Determination

There were no studies of $PM_{10-2.5}$ and metabolic effects in the 2009 PM ISA. A high quality epidemiologic study reporting an association between long-term $PM_{10-2.5}$ exposure and incident diabetes is now available (Puett et al., 2011). In addition, effects on glucose (Teichert et al., 2013) or insulin (Wolf et al., 2016) were observed in cross-sectional studies of glucose and insulin homeostasis conducted in European cohorts. Limited biological plausibility is derived from the potential for deposition of $PM_{10-2.5}$ to modulate the ANS, the immune system or disrupt glucose, lipid, and insulin homeostasis. The evidence relevant to the causal determination for long-term exposures to $PM_{10-2.5}$ is evaluated using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015). The key evidence, as it relates to the causal framework, is summarized in Table 7-15. **Overall, the evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposure and metabolic effects.**

Table 7-16 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between long-term $PM_{10-2.5}$ exposure and metabolic effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Evidence at least one high quality epidemiologic study but studies limited in number, overall.	Positive association with incident T2D reported in NHS; Effects on glucose and insulin homeostasis observed in cross-sectional analyses of European cohorts.	Puett et al. (2011) Teichert et al. (2013) Wolf et al. (2016)	Mean concentrations across studies 6.2–34.0 $\mu g/m^3$
Uncertainty regarding epidemiologic evidence from copollutant models to support and independent $PM_{10-2.5}$ association	$PM_{10-2.5}$ association persisted after adjustment for $PM_{2.5}$ but evidence lacking, overall.	Puett et al. (2011)	
Uncertainty regarding exposure measurement error	$PM_{10-2.5}$ concentrations estimated using difference of monthly modelled concentrations of PM_{10} and $PM_{2.5}$ which has noted limitations.	Section 2.4.2	
	Potentially uncharacterized spatial variation adds additional uncertainty.	Section 2.5 and Section 3.3.1.1	
Limited biological plausibility	Some evidence that $PM_{10-2.5}$ may modulate the ANS following deposition, the immune system or disrupt glucose, lipid, and insulin homeostasis.	Section 7.4.1	

$PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than a nominal diameter of 2.5 µm.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{10-2.5}$ concentrations with which the evidence is substantiated.

7.5 Short-Term UFP Exposure and Metabolic Effects

There are no experimental studies examining the effects short-term UFP exposure on metabolic function. A recent longitudinal analysis of the data from the HNR study found an association of 28-day

average accumulation mode UFP (NC) exposure with increased blood glucose [0.64 mg/dL (95% CI: 0.07, 1.21) per IQR increase] and increased HbA1c [0.03% (0.01, 0.05) per IQR increase] (Lucht et al., 2018a). Uncharacterized temporal and spatial variability in the exposure concentration is an uncertainty for this study because a 28-day average exposure was estimated for 1 km^2 grid cells, not the participants' residence (Section **Error! Reference source not found.**). **Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between short-term UFP exposure and metabolic effects.**

7.6 Long-Term UFP Exposure and Metabolic Effects

There were no studies of the effect of long-term UFP exposure and metabolic effects reviewed in the 2009 PM ISA. In a recent longitudinal epidemiologic study, Lucht et al. (2018a) reported an increase in FBG (0.67 mg/dL 0.10 1.24) and HbA1c [0.09% (0.07, 0.11) per IQR increase] in association with 91-day average exposure to accumulation mode UFP (NC). Uncharacterized spatial and temporal variability is an uncertainty in this study because UFP exposure was assigned to a 1 km^2 grid cell, not at the level of the participants' residence (Section **Error! Reference source not found.**). In addition, a toxicological study (Li et al., 2013) evaluated the effects of long-term UFP in mice (Table 7-16). This study investigated the effects of long-term UFP exposure in an *Ldlr*$^{-/-}$ mouse model fed a high fat diet in the presence or absence of an apolipoprotein A-I mimetic peptide (D-4F). This genetic mouse model has a mutation in the low-density lipoprotein receptor and are prone to very high blood cholesterol levels when fed a high fat diet. While the investigators identified UFP effects such as increased triglyceride, decreased HDL, reduced HDL antioxidant index, increased oxidized lipid metabolites (HETEs and HODEs), increased serum amyloid A (SAA) and TNFα, and increased area in atherosclerotic plaque lesions (all $p < 0.05$) that were improved by D-4F (a mimetic peptide of apolipoprotein A-I made of D-amino acids) administration, the authors did not include wild-type controls. Furthermore, there are inherent differences in cholesterol metabolism between mouse and human that render the mouse somewhat resistant to the development of atherosclerotic plaques. Specifically, mice lack cholesterol ester transfer protein that shuttles cholesterol from HDL to LDL for reverse cholesterol transport; therefore, mice carry most of their cholesterol on HDL particles rather than, like human, on LDL particles (Getz and Reardon, 2012). The available studies continue to be limited. **Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and metabolic effects.**

Table 7-17 Study specific details from animal toxicology studies of metabolic homeostasis.

Study	Study Population	Exposure Details	Endpoints Examined
Li et al. (2013)	*Ldlr*$^{-/-}$ mouse on C57Bl/6 background, male, 90 days old	Whole body inhalation of UFP collected in urban regions of Los Angeles, CA. Animals were exposed to 360 μg/m^3 for 10 weeks ± poA1 mimetic peptide	Plasma HDL, HDL oxidation index, paraoxonase activity. Plasma, 9-HODE and 12-HETE, SAA and TNF-α. In the aorta, Sudan IV staining for fatty streaks, both in en face and aortic leaflet preparations

7.7 Reference

ADA (American Diabetes Association). (2014). Diagnosis and classification of diabetes mellitus. Diabetes Care 37 Suppl 1: S81-S90. http://dx.doi.org/10.2337/dc14-S081

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CHAPTER 8 NERVOUS SYSTEM EFFECTS

Summary of Causality Determinations for Short- and Long-Term Particulate Matter (PM) Exposure and Nervous System Effects

This chapter characterizes the scientific evidence that supports causality determinations for short- and long-term PM exposure and nervous system effects. The types of studies evaluated within this chapter are consistent with the overall scope of the ISA as detailed in the Preface (see Section 11P.3.1). In assessing the overall evidence, strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix. More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2015).

Size Fraction	Causality Determination
Short-term Exposure	
$PM_{2.5}$	Suggestive of, but not sufficient to infer
$PM_{10-2.5}$	Inadequate
UFP	Suggestive of, but not sufficient to infer
Long-term Exposure	
$PM_{2.5}$	Likely to be causal
$PM_{10-2.5}$	Suggestive of, but not sufficient to infer
UFP	Likely to be causal

8.1 Short-term $PM_{2.5}$ Exposure and Nervous System Effects

The evidence in the 2009 ISA for PM was characterized as "inadequate" to determine if a causal relationship between short-term $PM_{2.5}$ exposure and nervous system effects exists (U.S. EPA, 2009). A small number of experimental animal studies relevant to the assessment were available for review. Exposure to $PM_{2.5}$ CAPs resulted in pro-inflammatory responses in the brain (Campbell et al., 2005) and modulation of norepinephrine and corticosterone levels, which are indicative of sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) stress axis activation (Sirivelu et al., 2006). Studies found that exposure to $PM_{2.5}$ CAPs could affect the autonomic nervous system (ANS) by activating sensory nerves in the respiratory tract, leading to cardiac oxidative stress and changes in cardiac function (Ghelfi et al., 2008; Rhoden et al., 2005). In addition, multiple studies reported that short-term exposure to $PM_{2.5}$ is associated with changes in heart rate variability (HRV), which reflect an imbalance between the sympathetic and parasympathetic arms of the ANS (Section 6.1.1). Findings from

recent experimental studies are generally consistent with previous studies, adding to the evidence that short-term exposure to $PM_{2.5}$ can lead to brain inflammation and activation of the SNS. The small number of epidemiologic studies published since the 2009 PM ISA do not consistently report positive associations between short-term exposure to $PM_{2.5}$ and hospitalizations for nervous system diseases, depression, or reduced cognitive function.

The discussion of short-term $PM_{2.5}$ exposure and nervous system effects opens with a discussion of biological plausibility (Section 8.1.1) that provides background for the subsequent sections in which groups of related endpoints are presented in the context of relevant disease pathways. These outcome groupings are activation of the SNS and HPA stress Axis (Section 8.1.2), brain inflammation and oxidative stress (Section 8.1.3), and diseases of the nervous system and depression (Section 8.1.4). Evidence pertaining to $PM_{2.5}$ components is summarized in Section 8.1.5. Finally, the collective body of evidence is integrated[71] across and within scientific disciplines, and the rationale for the causality determination is outlined in Section 8.1.6.

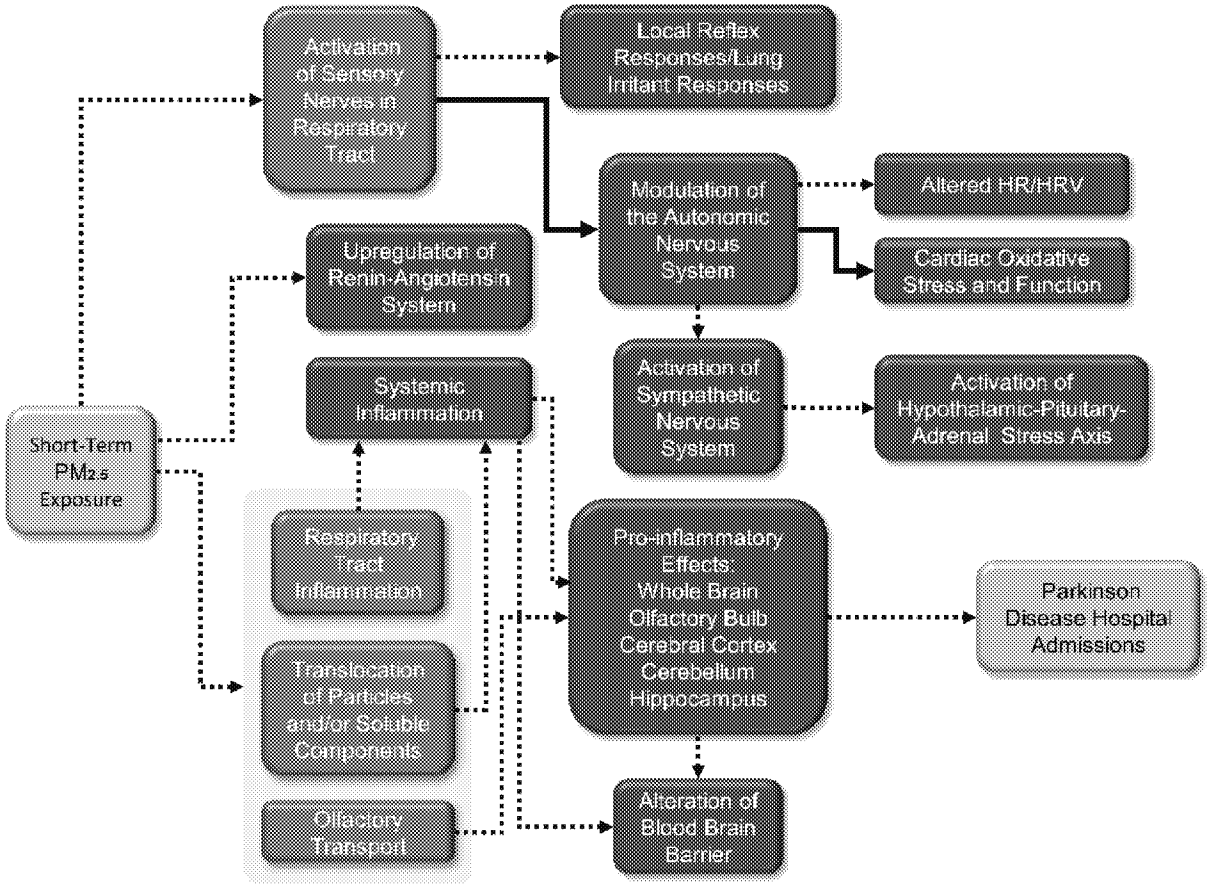
8.1.1 Biological Plausibility

This section describes biological pathways that potentially underlie the development of nervous system effects resulting from short-term exposure to $PM_{2.5}$. Figure 8-1 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" short-term exposure to $PM_{2.5}$ may lead to nervous system effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 8.1.

Once $PM_{2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see Chapter 4). $PM_{2.5}$ and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate reactive oxygen species (ROS) and this capacity is termed "oxidative potential". Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to health effects. Inflammatory mediators may diffuse from the respiratory tract into the systemic circulation and lead to inflammation in extrapulmonary compartments (Section 6.1.1). Soluble components of $PM_{2.5}$, and poorly soluble particles

[71] As detailed in the Preface, risk estimates are for a 10 $\mu g/m^3$ increase in 24-hour avg $PM_{2.5}$ concentrations unless otherwise noted.

that are part of the $PM_{2.5}$ fraction and smaller than approximately 200 nm, may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. A fraction of $PM_{2.5}$ may deposit on the olfactory epithelium. Soluble components of $PM_{2.5,}$ and poorly soluble particles that are part of the $PM_{2.5}$ fraction and smaller than approximately 200 nm, may also be transported via the olfactory nerve to the olfactory bulb of the brain. The extent to which translocation into the systemic circulation or transport to the olfactory bulb occurs is currently uncertain. For further discussion of translocation and olfactory transport, see Chapter 4.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Solid arrows denote direct evidence of the relationship as provided, for example, by an inhibitor of the pathway or a genetic knock-out model used in an experimental study. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 8-1 Potential biological pathways for nervous system effects following short-term $PM_{2.5}$ exposure.

Evidence that short-term exposure to $PM_{2.5}$ may affect the nervous system generally informs two different pathways (Figure 8-1). The first pathway begins with the activation of sensory nerves in the respiratory tract that can trigger local reflex responses and transmit signals to regions of the central nervous system that regulate autonomic outflow. Altered autonomic tone may result in downstream systemic effects. The second pathway begins with pulmonary inflammation and may lead to systemic inflammation and to inflammation in the brain. Inflammation may lead to a worsening of neurodegenerative disease. Evidence for these pathways is described below.

Activation of Sensory Nerves and Modulation of the Autonomic Nervous System (ANS)

With regard to the first pathway, activation of sensory nerves in the respiratory tract leads to modulation of the sympathetic and parasympathetic branches of the ANS. The ANS influences all the internal organs, including the heart. Lung irritant responses, discussed in Chapter 5 (Section 5.1.1, Section 5.1.7, and Section 5.1.8), are local reflex responses triggered by $PM_{2.5}$ exposure-induced activation of sensory nerves. Altered autonomic outflow can manifest as changes in heart rate and heart rate variability, as discussed in Section 6.1.1. Furthermore, an animal toxicological study demonstrated that specific receptors on the sensory nerves, the transient receptor potential (TRP) cation channels, were involved in mediating autonomic responses in the heart (Ghelfi et al., 2008). Treatment with a receptor antagonist blocked cardiac oxidative stress and changes in electrophysiologic parameters resulting from short-term exposure to $PM_{2.5}$. Inhibitors of the parasympathetic nervous system and SNS also blocked cardiac oxidative stress in this model (Rhoden et al., 2005). The solid lines depicted in Figure 8-1, which connect activation of sensory nerves to modulation of the ANS and to cardiac oxidative stress/function, indicate that activation of TRP receptors on sensory nerves in the respiratory tract mediated changes in the heart via the ANS.

The SNS may be especially impacted by $PM_{2.5}$ exposure. Animal toxicological studies demonstrated that short-term $PM_{2.5}$ exposure results in increased norepinephrine in specific hypothalamic regions (Balasubramanian et al., 2013; Sirivelu et al., 2006) and in peripheral tissues (Chiarella et al., 2014). Increases in norepinephrine, both in the brain and peripheral organs, are hallmarks of increased SNS activity. Further, a neuroendocrine response, activation of the HPA stress axis, may be initiated in the hypothalamus via norepinephrine and corticotropin releasing hormone (CRH), resulting in increased levels of circulating glucocorticoids. Sirivelu et al. (2006) and Balasubramanian et al. (2013) found increased CRH levels in the hypothalamus, as well as increased serum glucocorticoids. Thus, short-term exposure to $PM_{2.5}$ may lead to activation of the SNS and to activation of the HPA stress axis.

Furthermore, studies suggest connections between modulation of the ANS resulting from short-term $PM_{2.5}$ exposure and other effects. A study in mice found that exposure to $PM_{2.5}$ increased SNS activity, as indicated by increased norepinephrine levels in the lung and in brown adipose tissue (Chiarella et al., 2014). Inhalation of $PM_{2.5}$ increased BALF cytokine levels, an effect which was enhanced by β2

adrenergic receptor agonists, which mimic the actions of norepinephrine. Using knock-out mice lacking the β2 adrenergic receptor specifically in alveolar macrophage, it was demonstrated that inhalation of $PM_{2.5}$ enhanced cytokine release from alveolar macrophages. This involvement of the SNS in inflammatory responses resulting from $PM_{2.5}$ exposure is depicted by the solid line that connects ANS responses and respiratory tract inflammation in Figure 5-1. This is likely to represent a positive feed-back mechanism by which the ANS may enhance inflammation. Another study found upregulation of the renin-angiotensin (RAS) system in the lung and heart (Aztatzi-Aguilar et al., 2015), as depicted in Figure 5-1. The SNS and RAS are known to interact in a positive feedback fashion (Section 8.2.1), with important ramifications for the cardiovascular system. However, it is not known whether SNS activation or some other mechanism mediated the changes in the RAS observed in the respiratory tract (Aztatzi-Aguilar et al., 2015). Ghelfi et al. (2010) found that short-term exposure to $PM_{2.5}$ increased levels of circulating angiotensin II, which is an important component of the RAS.

Inflammation

With regard to the second pathway, deposition of $PM_{2.5}$ in the respiratory tract may lead to pulmonary inflammation (see Section 5.1.1) and to systemic inflammation (see Section 6.1.1). Brain inflammation may be due to peripheral immune activation (Fonken et al., 2011) or to systemic circulation of $PM_{2.5}$, alone or engulfed by macrophages, that results in particle uptake in the brain (Ljubimova et al., 2013). Inflammation in the brain may alternatively occur following olfactory transport of poorly soluble particles or their soluble components or to a neuroendocrine stress response resulting from activation of the HPA stress axis (Kodavanti, 2016).

Several animal toxicological studies demonstrated pro-inflammatory effects following short-term $PM_{2.5}$ exposure (Campbell et al., 2005), (Bos et al., 2012), (Tyler et al., 2016). Inflammation was observed in the olfactory bulb, cerebral cortex, cerebellum, and hippocampus. Two of these studies demonstrated brain inflammation in the absence of pulmonary or systemic inflammation (Tyler et al., 2016; Bos et al., 2012), pointing to a direct effect of $PM_{2.5}$ on the brain. Evidence for perturbation of the blood brain barrier is provided by a controlled human exposure study (Liu et al., 2017). Circulating inflammatory mediators and soluble components of $PM_{2.5}$, as well as brain inflammation, may play a role in altering the blood brain barrier. Inflammation may lead to a worsening of neurodegenerative disease and provide support for epidemiologic evidence of hospitalization for Parkinson disease (Zanobetti et al., 2014).

Summary of Biological Plausibility

As described here, there are two proposed pathways by which short-term exposure to $PM_{2.5}$ may lead to nervous system effects. Experimental studies in animals and humans contribute all the evidence of upstream events. The first pathway begins with activation of sensory nerves in the respiratory tract and may potentially lead to modulation of the ANS resulting in increased activity of the SNS and stimulation

of the HPA stress axis. Upregulation of the RAS may also contribute to SNS activation. Thus, the ANS may mediate systemic responses due to exposure to $PM_{2.5}$. The second proposed pathway begins with pulmonary/systemic inflammation or olfactory transport of $PM_{2.5}$ leading to brain inflammation. This pathway provides biological plausibility for epidemiologic results of increased hospital admissions for Parkinson disease. These pathways will be used to inform a causality determination, which is discussed later in the chapter (Section 8.1.6).

8.1.2 Activation of the Sympathetic Nervous System and the Hypothalamic-Pituitary-Adrenal (HPA)Stress Axis

As discussed in the biological plausibility section above, sensory nerves in the respiratory tract can transmit signals to regions of the central nervous system that regulate autonomic outflow. The ANS regulates many different functions in the body (e.g., heart rate). Further, a neuroendocrine response, activation of the HPA stress axis, may be initiated in the hypothalamus via norepinephrine and CRH, resulting in increased levels of circulating glucocorticoids.

8.1.2.1 Controlled Human Exposure Study

A controlled human exposure study examined the effects of a 130 minute exposure to $PM_{2.5}$ CAPs in Toronto on urinary and blood biomarkers associated with neural effects (Liu et al., 2017). No association was observed with SNS or HPA stress axis-related biomarkers (Table 8-1).

Table 8-1 Study-specific details from a controlled human exposure study of short-term $PM_{2.5}$ exposure and activation of the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) stress axis.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Liu et al. (2017) Species: Human Health status: Healthy nonsmokers Sex: 29 females, 26 males Age: 18–60 yr Study design: Single-blind randomized cross-over trial	CAPs from Toronto, ON Particle sizes: 0.15–2.5 µm Control: HEPA filtered ambient air or HEPA-filtered medical air (ultrafine study)	Route: Face mask inhalation Dose/concentration: 238.4 ± 62.0 µg/m^3 Duration of exposure: 130 min Time to analysis: 1 and 21 h	Urinary and blood markers of neural effects

CAPs = concentrated ambient particles, h=hours, HEPA = high efficiency particulate air, yr=years.

8.1.2.2 Animal Toxicological Studies

An animal toxicological study included in the 2009 ISA PM (U.S. EPA, 2009) found that $PM_{2.5}$ CAPs exposure resulted in modulation of norepinephrine in the paraventricular nucleus of the hypothalamus and in the olfactory bulb of nonallergic rats, while rats that were sensitized and challenged with ovalbumin exhibited increases in dopamine in the medial preoptic area (Sirivelu et al., 2006). Increased norepinephrine levels in the hypothalamus indicate activation of the SNS and this study also found an increase in serum corticosterone in non-allergic $PM_{2.5}$ CAPs-exposed rats, suggesting an activation of the HPA stress axis subsequent to changes in these neurotransmitters. Recent studies provide additional support demonstrating an effect of $PM_{2.5}$ on the SNS and HPA stress axis (Table 8-2).

Balasubramanian et al. (2013) found that inhalation of $PM_{2.5}$ CAPs altered levels of neurotransmitters and CRH in specific brain regions of lean and obese rats. Lean Brown Norway rats exposed to $PM_{2.5}$ CAPs in Grand Rapids, MI had increased levels of norepinephrine in the paraventricular nucleus of the hypothalamus 1 day ($p < 0.05$), but not 3 days, after exposure. A similar pattern was observed for 5-hydroxy-indole acetic acid ($p < 0.05$), the main metabolite of serotonin, while dopamine levels were unchanged. An increase in CRH in the median eminence of the hypothalamus was found after 1 day ($p < 0.05$), but not 3 days, of $PM_{2.5}$ CAPs exposure. Corpulent JCR/LA rats exposed for 4 days to CAPs in Detroit, MI had increased norepinephrine and 5-hydroxy-indole acetic acid in the paraventricular nucleus ($p < 0.05$), while the amount of CRH in the median eminence was unchanged. Increased norepinephrine levels in the paraventricular nucleus of the hypothalamus indicate activation of the SNS, while increased CRH levels in the median eminence of the hypothalamus indicate activation of the HPA stress axis. Linkage between the SNS and the HPA stress axis occurs when norepinephrine in the paraventricular nucleus stimulates CRH neurons resulting in the release of CRH from the median eminence. Subsequently, circulating CRH stimulates adrenocorticotropin secretion from the pituitary and adrenocorticotropin acts on the adrenal gland resulting in the secretion of glucocorticoids such as corticosterone. Thus, activation of the SNS may lead to increased glucocorticoid levels. In the current study, an increase in norepinephrine was accompanied by an increase in CRH only in the lean rats exposed for 1 day to $PM_{2.5}$ CAPs.

Findings of Balasubramanian et al. (2013) build on the results of (Sirivelu et al., 2006) that found increases in norepinephrine levels in the paraventricular nucleus of the hypothalamus and in serum corticosterone levels following a 1-day exposure to CAPs. Together, these studies indicate that $PM_{2.5}$ exposure may increase the activity of the SNS and the HPA stress axis via effects on the hypothalamus. In Balasubramanian et al. (2013), increases in neurotransmitter levels were observed in obese animals, but they were not increased in the lean animals, following a multi-day exposure to $PM_{2.5}$. This raises the possibility that an adaptive response dampened the SNS and HPA stress axis in the lean, but not in the obese, animals.

Evidence for SNS activation following short-term exposure to $PM_{2.5}$ is also provided by (Chiarella et al., 2014). In this study, C57BL/6 mice were exposed to $PM_{2.5}$ CAPs in Chicago, IL for

several days. Norepinephrine levels in both lung and brown adipose tissue were increased above controls ($p < 0.05$), indicating activation of the SNS. Norepinephrine was found to enhance the amount of IL−6 in BALF, a pro-inflammatory effect, in the lung (see Section 5.1.7).

Table 8-2 Study-specific details from animal toxicological studies of short-term $PM_{2.5}$ exposure and activation of the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) stress axis.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Balasubramanian et al. (2013) Species: rat Strain: Brown Norway (lean) JCR/LA (corpulent) Sex: male Age/Weight: JCR/LA-4 and 8 mo	CAPs from urban Grand Rapids, MI or urban Detroit, MI Particle Sizes: $PM_{2.5}$ HEPA-filtered clean air	Route: Whole body inhalation Dose/Concentration: 1 day: mean 519 µg/m^3 $PM_{2.5}$ CAPs Grand Rapids 3 day: mean 595 µg/m^3 $PM_{2.5}$ CAPs 4 day: mean 291 µg/m^3 $PM_{2.5}$ CAPs Grand Rapids Duration of exposure: 1, 3, or 4 days Time to analysis: 24 h after the last exposure	Brain tissue—neurotransmitter and corticotrophin releasing hormone levels in the hypothalamus
Chiarella et al. (2014) Species: Mouse Sex: Male Strain: C57BL/6 WT and Adrb2 knockouts Age/Weight: 8−12 week	CAPs from Chicago, IL Particle size: $PM_{2.5}$ Control: filtered ambient air	Route: Whole body inhalation Dose/Concentration: 109.1 ± 6.1 µg/m^3 Duration: 8 h/day for 3 days	BALF and lung tissue—IL−6, norepinephrine Brown adipose tissue • norepinephrine Liver tissue • prothrombin and TF mRNA Thrombotic potential

Adrb2 = adrenergic beta 2, BALF = bronchoalveolar lavage fluid, CAPs = concentrated ambient particles, h=hour(s), HEPA=high efficiency particulate air, IL−6 = interleukin−6; TF = tissue factor; WT = wild type.

8.1.3 Brain Inflammation and Oxidative Stress

Chronic brain inflammation is thought to underlie conditions such as neurodegenerative disease. Although repeated exposure may lead to similar downstream health consequences, the effect of acute inflammation is less clear.

8.1.3.1 Controlled Human Exposure Study

A controlled human exposure study examined the effects of a 130 minute exposure to $PM_{2.5}$ CAPs in Toronto, ON on urinary and blood biomarkers associated with neural effects (Liu et al., 2017). An association was observed between exposure to $PM_{2.5}$ CAPs and blood ubiquitin C-terminal hydrolase L1, a biomarker related to blood brain barrier integrity, measured 21 hours post-exposure ($p < 0.1$). Impaired blood brain barrier integrity is associated with brain inflammation (Table 8-3).

Table 8-3 Study-specific details from a controlled human exposure study of short-term $PM_{2.5}$ exposure and brain inflammation and oxidative stress.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Liu et al. (2017) Species: Human Health status: Healthy nonsmokers Sex: 29 females, 26 males Age: 18–60 yr Study design: Single-blind randomized cross-over trial	CAPs from Toronto, ON Particle sizes: 0.15–2.5 µm Control: HEPA filtered ambient air or HEPA-filtered medical air (ultrafine study)	Route: Face mask inhalation Dose/concentration: 238.4 ± 62.0 µg/m^3 Duration of exposure: 130 min Time to analysis: 1 and 21 h	Urinary and blood markers of neural effects

CAPs = concentrated ambient particles, h=hour(s), HEPA = high efficiency particulate absorber, min=minute.

8.1.3.2 Animal Toxicological Studies

An animal toxicological study included in the 2009 PM ISA (U.S. EPA, 2009) provided evidence that short-term exposure to $PM_{2.5}$ can lead to brain inflammation. In this study, Campbell et al. (2005) found that $PM_{2.5}$ CAPs exposure enhanced pro-inflammatory responses including cytokine levels and NFκB activation in the brain of animals that had been sensitized and challenged with ovalbumin. Recent studies of short-term exposure to $PM_{2.5}$ add to the evidence base reporting findings that are consistent with brain inflammation (Table 8-4).

Several recent studies examined the effects of traffic-related $PM_{2.5}$ on gene expression in the brain. In one of these, 2 groups of C57BL/6 mice were placed in a highway tunnel (Antwerp, Belgium) for 5 days in cages with and without a highly efficient particle filter (Bos et al., 2012). Other groups of animals were housed in a building near the tunnel in a cage with a less efficient particle filter and in a cage in the animal facility. Bronchoalveolar lavage was performed and demonstrated the presence of carbon particles in alveolar macrophages only in the animals exposed to unfiltered tunnel air. No evidence

of pulmonary (i.e., bronchoalveolar lavage fluid (BALF) cell counts, histology) or systemic inflammation (i.e., coagulation parameters in blood) was found. Alterations in gene expression were observed in the hippocampus and olfactory bulb of animals exposed to unfiltered tunnel air compared with controls. In the hippocampus, this included upregulation of COX2, NOS2, and NOS3 compared to the group exposed to filtered tunnel air and upregulation of COX2, NOS2, and NFE2L2 compared to the group exposed to the building air ($p < 0.05$). In the olfactory bulb, this included downregulation of IL−2α, COX2, NFE2L2, and BDNF compared to the group exposed to filtered tunnel air and downregulation of IL−2α, COX2, and IL−6 compared to the group exposed to the building air ($p < 0.05$). Some differences in gene expression were noted between responses in the control group exposed to filtered tunnel air and the control group exposed to building air, indicating that upregulation of COX2 in hippocampus and downregulation of IL−6 in olfactory bulb may have been due to confounders such as noise stress.

A second study also found evidence of brain inflammation following short-term exposure to $PM_{2.5}$. Tyler et al. (2016) exposed C67BL/6 and ApoE knockout mice to resuspended diesel exhaust particles (DEP) for 6-hours and found decreased mRNA levels for IL−6 and TGF-β in hippocampus of C67BL/6 mice ($p < 0.05$) and increased mRNA levels for IL−6, TGF-β, and TNFα in hippocampus of ApoE knockout mice ($p < 0.05$). In contrast, no inflammatory effects were seen in BALF (see Section 5.1.7.3). Another study examined changes in global gene expression in the brain, as well as expression of Arc and Rac genes and their protein products, in Fischer 344 rats exposed to CAPs in Riverside, CA for 2 weeks (Ljubimova et al., 2013). Exposure to CAPs did not induce any changes in gene or protein expression.

Table 8-4 Study-specific details from animal toxicological studies of short-term $PM_{2.5}$ exposure and brain inflammation and oxidative stress.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Bos et al. (2012) Species: Mouse Sex: Male Strain: C57BL/6 Age/Weight: 10–12 weeks	Ambient PM– Tunnel in Antwerp, Brussels Particle size: $PM_{2.5}$ Controls: 1) HEPA-filtered tunnel air 2) Ambient air in building near roadside	Route: Whole body inhalation Dose/Concentration: Mean 55.1 µg/m³ $PM_{2.5}$ Duration: 5 days Time to analysis: immediately after exposure	Gene expression of inflammatory-related proteins in hippocampus and olfactory bulb BALF cell counts Blood coagulation parameters Lung histology
Ljubimova et al. (2013) Species: Rat Sex: Male Strain: Fisher 344 Age/Weight: 3–7 weeks	CAPs from Riverside, CA (summer) Particle size: 0.18–2.5 µm Control: Filtered air	Route: Whole body inhalation Dose/Concentration: 149 ± 24 µg/m³ Particle number: 67 ± 6 particles/cm³ 10–3 Duration: 5 h/day, 4 days/week for 0.5 mo	Brain tissue—Immunohistochemistry Gene expression—mRNA
Tyler et al. (2016) Species: Mouse Strain: C67BL/6 and ApoE knockout Age/Weight: 6–8 weeks	DEP, resuspended Particle Size: 1.5–3.0 µm ± 1.3–1.6 µm Control: filtered air	Route: Whole body inhalation Dose/Concentration: 315.3 ± 50.7 µg/m³ Duration: 6 h Time to analysis: overnight	Hippocampal tissue: cytokine mRNA expression

ApoE = apolipoprotein E, CAPs = concentrated ambient particles, DEP = diesel exhaust particle, h=hour(s), HEPA = high efficiency particulate absorber.

8.1.4 Diseases of the Nervous System and Depression

A small number of epidemiologic studies of short-term exposure to $PM_{2.5}$ and nervous system outcomes were conducted since the 2009 PM ISA (U.S. EPA, 2009) was published (Table 8-5). A large U.S. study of Medicare enrollees reported an association with Parkinson Disease [RR: 1.03 (95%CI: 1.01, 1.05)] but not dementia or Alzheimer's disease (Zanobetti et al., 2014). Although only the primary ICD code was used to identify Parkinson disease hospitalizations, the specific reason for the admission is not clear and could reflect a range of complications experienced by Parkinson disease patients. No association of short-term $PM_{2.5}$ exposure with dementia related hospital admissions was reported in a smaller study in Madrid, Spain (quantitative results not presented) (Linares et al., 2017).

Studies of short-term exposure to $PM_{2.5}$ and depression also add to the still limited evidence base. No overall increase in hospital admissions for depressive symptoms was observed in a Canadian study (Szyszkowicz, 2007), although associations were detected in some subgroups (i.e., among females during the cold season [RR: 1.12 (95%CI: 1.03, 1. 21)]). Wang et al. (2014) reported a decrease in depressive

symptoms among older adults enrolled in the Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston (MOBILIZE) study [OR: 0.31 (95%CI: 0.10, 0.94)] in association with $PM_{2.5}$ exposure averaged over 14 days preceding the assessment.

Finally, a study of neuropsychological function in children was conducted at home and at school. In this study, short-term exposure (lagged 0−48 hours), was associated with some of the tests of administered, including those for processing speed (Saenen et al., 2016).

Table 8-5 Epidemiologic studies examining the association between short-term $PM_{2.5}$ exposures and nervous system effects.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Zanobetti et al. (2014) 121 Communities, U.S. 1999–2010	Medicare >65 yr old	2-day avg for community, 1 or more monitors	NR (community specific only)	HAED visits for Parkinson disease (ICD9: 332), Alzheimer's disease (ICD9: 331.0), Dementia (ICD9: 230)	Correlations (r): NR Copollutant models: NR
†Wang et al. (2014) Boston, MA	MOBILIZE N = 732 Older adults	1 monitor, 14-day avg prior to outcome assessment	Mean (SD) 8.6 (4.9)	CESD-R ≤ 16 (depressive symptoms)	Correlations (r): NR Copollutant models: NR
†Linares et al. (2017) Madrid, Spain 2001–2009	60 plus yr old N = 1,175	24 h avg, lag 0–5, 27 urban monitors	Mean (SD) 17.1 (7.82)	Dementia-related HAED visits (ICD9: 290–294 except 291.0 and 292.0)	Correlations (r): NR Copollutant models: NR
Szyszkowicz (2007) Edmonton Canada 1992–2002	Capital Health System patients for 5 hospitals	24 h avg, lags 0, 1 and 2 days 1 monitor	Mean 8.5 IQR 6.2	HAED Visit Depression (ICD9: 311)	Correlations (r): NR Copollutant models: NR

Table 8-5 (Continued): Epidemiologic studies examining the association between short-term $PM_{2.5}$ exposures and nervous system effects.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutant Examination
†Saenen et al. (2016) Flanders, Belgium	COGNAC Children	Daily avg, spatiotemporal model (satellite, land cover and monitor data), at school and at residential address, lags 0–2 days R2 > 0.80	Residence: Median 16.5 (IQR: 18.9) School: Median 5.14 (IQR: 8.85)	Attention: continuous performance, Stroop Memory: digit span forward, digit span backward Visual processing speed: digit symbol, pattern comparison	Correlations (r): NR Copollutant models: NR

COGNAC = Cognition and Air Pollution in Children study, CESD-R = Center for Epidemiological Studies Depression Scale, HAED = Hospital Admission Emergency Department, ICD9 = International Classification of Disease 9th revision, MOBILIZE = Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston; NR = Not Reported; yr=year

†Studies published since the 2009 PM ISA.

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8.1.5 Components and Sources of $PM_{2.5}$

There are few studies examining components or sources of $PM_{2.5}$ in relation to nervous system effects (Table 8-6). Decreased scores on some of the neurobehavioral tests (e.g., pattern comparison) with increasing 24 hour black carbon (BC) exposure (lagged 0–2 days) were observed in the study by Saenen et al. (2016). Saenen et al. (2016) observed associations with processing speed were observed in association with short-term $PM_{2.5}$ exposure in this study. Wang et al. (2014) did not find evidence indicating that BC exposure is associated with depressive symptoms among older adults in the Boston MOBILIZE study [OR: 1.0 (95%CI: 0.75, 1.33)]. The results of the studies included in this section that pertain to exposure to $PM_{2.5}$ are found in Section 8.1.4.

Table 8-6 Studies of the association between short-term exposure to $PM_{2.5}$ components and nervous system effects.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Saenen et al. (2016) Flanders, Belgium	COGNAC Children	Daily avg, spatiotemporal model (satellite, land cover and monitor data), at school and at residential address, lags 0–2 days R2 = 0.74	BC Median: 1.54 IQR: 0.20	Attention: continuous performance, Stroop Memory: digit span forward, digit span backward Visual processing speed: digit symbol, pattern comparison	Correlations (r): NR Copollutant models: NR
†Wang et al. (2014) Boston, MA	MOBILIZE N = 732 Older adults	1 monitor, 14-day avg prior to outcome assessment	BC Mean (SD): 0.62 (0.35) SO_4^{2-} Mean (SD): 2.6 (2.1)	CESD-R ≤ 16 (depressive symptoms)	Correlations (r): NR Copollutant models: NR

CESD-R = Center for Epidemiological Studies Depression Scale; COGNAC = Cognition and Air Pollution in Children study; MOBILIZE = Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston; NR = Not Reported

†Studies published since the 2009 PM ISA.

8.1.6 Summary and Causality Determination

The evidence reviewed in the 2009 PM ISA was characterized as "inadequate to infer" a causal relationship between short-term exposure and nervous system effects. Recent studies strengthen the evidence that short-term exposure to $PM_{2.5}$ can affect the nervous system.

Effects on the ANS and downstream consequences on the heart were observed in toxicological studies (Section 8.1.1). In addition, changes in hypothalamic neurotransmitters, including norepinephrine, and CRH were found in a study of mice exposed to $PM_{2.5}$ CAPs (Balasubramanian et al., 2013), and add to evidence described in the 2009 PM ISA of increased norepinephrine in the hypothalamus and olfactory bulb and increased serum corticosterone (Sirivelu et al., 2006). Such evidence that $PM_{2.5}$ exposure leads to changes in norepinephrine indicates that the hypothalamus plays an important role in mediating effects such as activation of the SNS and the HPA stress axis. Preliminary evidence shows a dampening of these responses after repeated exposures in lean, but not obese animals. Findings that short-term exposure to $PM_{2.5}$ results in altered expression of proinflammatory and antioxidant genes in hippocampus and olfactory bulb regions, in the absence of pulmonary or systemic inflammation, point to a direct effect of $PM_{2.5}$ on the brain (Tyler et al., 2016; Bos et al., 2012). They build on evidence, described in the 2009 PM ISA, of increased cytokines and NFκB activation in the cortex following short-term $PM_{2.5}$ CAPs exposure (Campbell et al., 2005). The evidence from epidemiologic studies that focus on specific diseases of the nervous system, however, remains limited. The evidence for the relationship between short-term exposure to $PM_{2.5}$ and effects on the nervous system is summarized in Table 8-7, using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015). With regard to the epidemiologic studies relating to short-term exposure to $PM_{2.5}$ and diseases of the nervous system or depression, the evidence is limited to a small number of analyses. Positive associations were not observed in studies of hospital admissions for depression, dementia, or Alzheimer's disease. A small increase in hospital admissions for Parkinson disease was reported in a large national study of Medicare recipients indicating that short-term exposure to $PM_{2.5}$ may exacerbate a range of symptoms experienced by Parkinson disease patients (Zanobetti et al., 2014). Finally, a study of school children reported associations with some tests of neuropsychological function. There was no consideration of confounding by copollutant exposures in these epidemiologic studies and studies of components were limited in number.

The strongest evidence to indicate an effect of short-term exposure to $PM_{2.5}$ on the nervous system is provided by experimental animal studies that show effects on the brain. Toxicological studies demonstrate changes in neurotransmitters in the hypothalamus that are linked to SNS and HPA stress axis activation, as well as upregulation of inflammation-related genes, changes in cytokine levels, and NFkB activation that are indicative of brain inflammation. In addition, an association of short-term $PM_{2.5}$ exposure with hospital admissions for PD was observed indicating the potential for exacerbation of the

disease. **Overall, the collective evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term exposure to $PM_{2.5}$ and nervous system effects.**

Table 8-7 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{2.5}$ exposure and nervous system effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Brain Inflammation and Oxidative Stress			
Evidence from toxicological studies at relevant $PM_{2.5}$ concentrations	Activation of NFκB and increased levels of cytokines Altered expression of pro-inflammatory/antioxidant genes in the absence pulmonary or systemic inflammation	Campbell et al. (2005) †Bos et al. (2012) †Tyler et al. (2016)	441.7 µg/m^3 55.1 µg/m^3 315.3 µg/m^3
Activation of the Sympathetic Nervous System and Hypothalamic-Pituitary-Adrenal Stress Axis			
Evidence from toxicological studies at relevant $PM_{2.5}$ concentrations	Increased levels of norepinephrine and CRH in hypothalamus and corticosterone in serum; Increased levels of norepinephrine in BALF and BAT	(Sirivelu et al., 2006) †(Balasubramanian et al., 2013) †Chiarella et al. (2014)	500 µg/m^3 219–595 µg/m^3 109.1 µg/m^3
Evidence from multiple studies report changes in HRV	Evidence across disciplines taken together supports changes in HRV that indicate ANS imbalance	Section 6.1.10	
Biological Plausibility			
Biological plausibility for effects related to the ANS and brain inflammation	Evidence for downstream CV events related to the ANS is stronger than evidence for downstream nervous system events related to inflammation		

Table 8-7 (Continued): Summary of evidence that is suggestive of, but not sufficient to infer a causal relationship between short-term $PM_{2.5}$ exposure and nervous system effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Diseases of the Nervous System and Depression			
Limited evidence of positive associations from epidemiologic studies	No associations with dementia or Alzheimer's disease HAED Association with PD HAED	†Zanobetti et al. (2014) †Linares et al. (2017) †Zanobetti et al. (2014)	NR 17.1
	Inverse or null associations with depressive symptoms or HAED for depression	†Wang et al. (2014) Szyszkowicz (2007)	8.6 8.5
	Associations with some tests of neuropsychological function (e.g., processing speed.	†Saenen et al. (2016)	
Uncertainty regarding confounding by copollutants	No epidemiologic studies reported findings from 2 pollutant models.	Section 8.1.4	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is characterized.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated (for experimental studies, ≤2 mg/m^3).

†Studies published since the 2009 PM ISA.

8.2 Long-term $PM_{2.5}$ Exposure and Nervous System Effects

The 2009 PM ISA described the limited available studies of the effects of long-term exposures to $PM_{2.5}$ on the nervous system (U.S. EPA, 2009). A study in mongrel dogs from two areas of Mexico with contrasting air pollution levels ($PM_{2.5}$ annual average concentration 21.5 μg/m^3 versus <15 μg/m^3) reported inflammation and stress protein responses in the brain, but had limitations stemming from its ecological design (Calderón-Garcidueñas et al., 2003). Another study found Parkinson disease-like brain histopathology following long-term exposure to $PM_{2.5}$ CAPs in ApoE knockout mice (Veronesi et al., 2005). There were no epidemiologic studies of long-term exposure to $PM_{2.5}$ although an analysis of NHANES III respondents reported an association between annual average PM_{10} concentration and cognitive function, which was approximately null after adjustment for race or ethnicity and SES (Chen and Schwartz, 2009). Recent studies add to the information, specifically strengthening the lines of evidence indicating that long-term exposure to $PM_{2.5}$ can lead to effects on the brain associated with neurodegeneration (i.e., neuroinflammation and reductions in brain volume), as well as cognitive effects in older adults.

The discussion of long-term $PM_{2.5}$ exposure and nervous system effects opens with a discussion of biological plausibility (Section 8.1.1) that provides background for the subsequent sections in which groups of related endpoints are presented in the context of relevant disease pathways. These outcome groupings are activation of the SNS and HPA stress Axis (Section 8.1.2), brain inflammation and oxidative stress (Section 8.1.3), morphologic changes in the brain (Section 8.2.4), cognitive and behavioral effect (Section 8.2.5), neurodegenerative diseases (Section 8.2.6) and neurodevelopmental effects (Section 8.2.7). Evidence pertaining to $PM_{2.5}$ components is summarized in Section 8.2.8. Finally, the collective body of evidence is integrated[72] across and within scientific disciplines, and the rationale for the causality determination is outlined in Section 8.1.6.

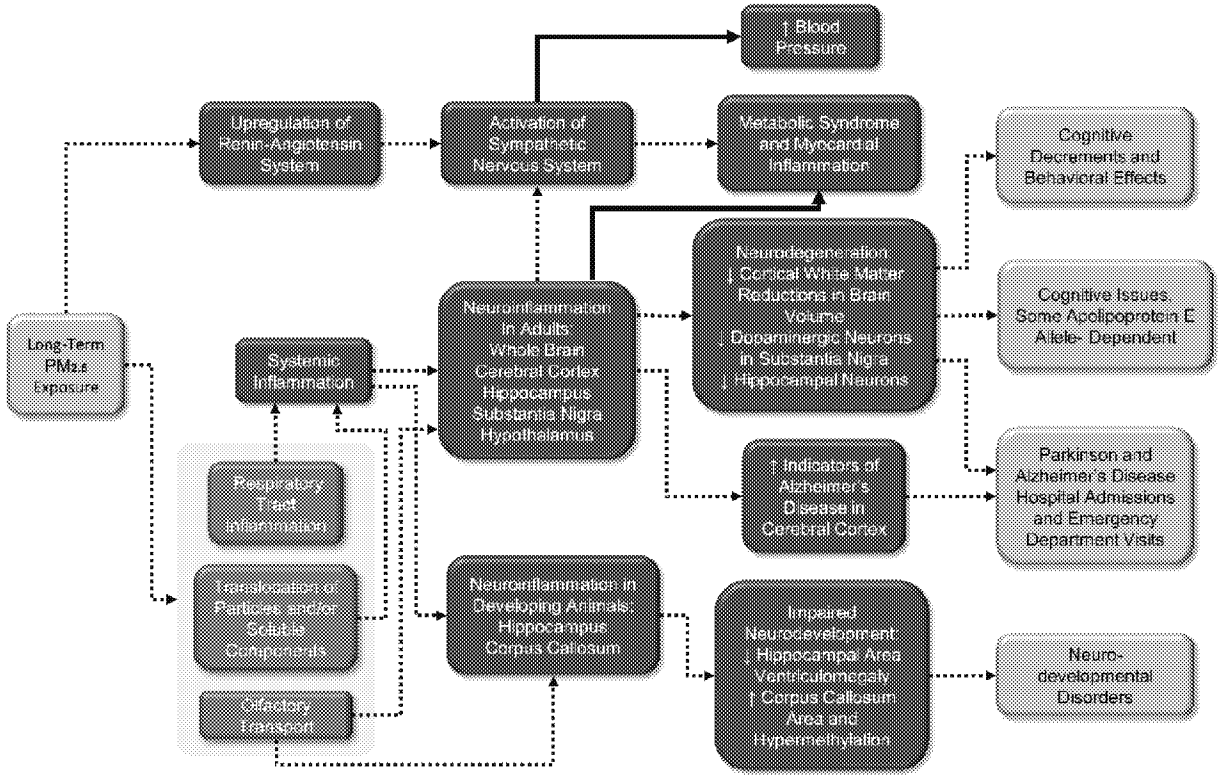
8.2.1 Biological Plausibility

This section describes biological pathways that potentially underlie the development of nervous system effects resulting from long-term exposure to $PM_{2.5}$. Figure 8-2 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" long-term exposure to $PM_{2.5}$ may lead to nervous system effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 8.2.

Once $PM_{2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see Chapter 4). $PM_{2.5}$ and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate reactive oxygen species (ROS) and this capacity is termed "oxidative potential". Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see Chapter 4). Immune system responses due to the presence of particles in the interstitial space may contribute to health effects. Inflammatory mediators may diffuse from the respiratory tract into the systemic circulation and lead to inflammation in extrapulmonary compartments (Section 6.2.1). Soluble components of $PM_{2.5,}$ and poorly soluble particles that are part of the $PM_{2.5}$ fraction and smaller than approximately 200 nm, may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. A fraction of $PM_{2.5}$ may deposit on the olfactory epithelium. Soluble components of $PM_{2.5,}$ and poorly soluble particles that are part of the $PM_{2.5}$ fraction and smaller than approximately 200 nm, may also be transported via the olfactory nerve to the olfactory bulb of the brain. The extent to which translocation

[72] As detailed in the Preface, risk estimates are for a 5 μg/m3 increase in annual PM2.5 concentrations unless otherwise noted.

into the systemic circulation or transport to the olfactory bulb occurs is currently uncertain. For further discussion of translocation and olfactory transport, see Chapter 4.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Solid arrows denote direct evidence of the relationship as provided, for example, by an inhibitor of the pathway or a genetic knock-out model used in an experimental study. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 8-2 Potential biological pathways for nervous system effects following long-term $PM_{2.5}$ exposure.

Evidence that long-term exposure to $PM_{2.5}$ may affect the nervous system generally informs two different pathways (Figure 8-2). The first pathway involves activation of the SNS, possibly by upregulation of the RAS. This pathway may lead to downstream systemic effects. The second pathway begins with pulmonary inflammation, leading to systemic inflammation and resulting in neuroinflammation. Neurodegenerative and neurodevelopmental disorders may be downstream effects of neuroinflammation. Evidence for both pathways is described below.

Upregulation of the Renin-Angiotensin (RAS) and Activation of the Sympathetic Nervous System (SNS)

With regard to the first pathway, activation of the SNS resulting from long-term $PM_{2.5}$ exposure may occur secondarily to RAS upregulation. Unlike the case of short-term exposure to $PM_{2.5}$, there is a lack of evidence that long-term $PM_{2.5}$ exposure results in activation of sensory nerves in the respiratory tract. However, animal toxicological studies support a role for the RAS. Aztatzi-Aguilar et al. (2016); Aztatzi-Aguilar et al. (2015) demonstrated that long-term exposure to $PM_{2.5}$ upregulates components of the RAS in the heart, lung, and kidneys (Section 5.2.8 and Section 6.2.7.2). Interaction between SNS and the RAS has important ramifications for cardiovascular health and disease. Angiotensin II enhances the release of norepinephrine from sympathetic nerve endings via the angiotensin 1 receptor (Brasch et al., 1993). SNS activation, in turn, stimulates secretion of the angiotensin II precursor protein, renin, from the kidney, thus providing positive feedback for the pathway (Gordon et al., 1967). Evidence that increased SNS activity leads to hypertension following long-term $PM_{2.5}$ CAPs exposure was provided by Ying et al. (2014). In this study, acute inhibition of the SNS resulted in decreased blood pressure. The solid line depicted in Figure 8-2 that connects activation of the SNS and increased blood pressure indicates that the SNS mediates the increase blood pressure observed following long-term exposure to $PM_{2.5}$.

Inflammation

With regard to the second pathway, deposition of $PM_{2.5}$ in the respiratory tract may lead to pulmonary inflammation (see Section 5.2.1) and to systemic inflammation (see Section 6.2.1), which in turn may lead to neuroinflammation. This could be due to peripheral immune activation (Fonken et al., 2011) or to systemic circulation of $PM_{2.5}$, alone or engulfed by macrophages, that results in particle uptake in the brain (Ljubimova et al., 2013). Neuroinflammation may alternatively occur following olfactory transport of poorly soluble particles or their soluble components or to a neuroendocrine stress response resulting from activation of the HPA stress axis (Kodavanti, 2016).

Several animal toxicological studies in adult rodents demonstrated neuroinflammation in the cerebral cortex, hippocampus, substantia nigra, and hypothalamus following $PM_{2.5}$ exposure (Tyler et al., 2016; Hogan et al., 2015; Ying et al., 2015; Liu et al., 2014; Ying et al., 2014; Fonken et al., 2011; Veronesi et al., 2005). One study found hippocampal inflammation in the absence of pulmonary inflammation (Tyler et al., 2016). Another found that inflammation in the hypothalamus, but not in the lung, was reversed following cessation of exposure (Ying et al., 2015). Evidence for a link between hypothalamic inflammation and peripheral effects was provided by animal toxicological studies using an inhibitor of inflammation (Zhao et al., 2015; Liu et al., 2014). The solid line depicted in Figure 8-2, which connects neuroinflammation with metabolic syndrome and with myocardial inflammation, indicates that hypothalamic inflammation mediates these peripheral effects following long-term exposure to $PM_{2.5}$. Hypothalamic inflammation may possibly activate the SNS (Ying et al., 2014).

In animal toxicological studies, neuroinflammation and astrocyte activation (an index of injury) were observed in specific brain regions following long-term exposure to $PM_{2.5}$. These responses were accompanied by neurodegeneration in those regions, which included the hippocampus (Hogan et al., 2015; Fonken et al., 2011) and the substantia nigra (Veronesi et al., 2005). Hippocampal changes occurred in conjunction with impaired learning and memory and with behavioral issues. Lesions in the substantia nigra are hallmarks of Parkinson disease. In addition, an animal toxicological study found increased markers of Alzheimer's disease in the cerebral cortex (Bhatt et al., 2015). Epidemiologic studies observed associations between exposure to $PM_{2.5}$ and decreases in cortical white and gray matter and in cerebral brain volume (Casanova et al., 2016; Chen et al., 2015; Wilker et al., 2015). Epidemiologic studies also provide evidence of cognitive impairment and Alzheimer's and Parkinson disease in association with exposure to $PM_{2.5}$ (Section 8.2.6).

Neuroinflammation may potentially lead to neurodevelopmental disorders in developing animals. In an animal toxicological study, prenatal exposure to $PM_{2.5}$ resulted in neuroinflammation in the hippocampus and corpus callosum (Klocke et al., 2017). These changes were sex-specific, occurring only in males. Morphologic changes, which were not sex-specific, were found in these same brain regions and were accompanied by enlarged lateral ventricles (i.e., ventriculomegaly). This study suggests a link between exposure to $PM_{2.5}$ and neurodevelopmental disorders; however, there was no evidence of cognitive or behavioral effects.

Summary of Biological Plausibility

As described here, there are two proposed pathways by which long-term exposure to $PM_{2.5}$ may lead to nervous system effects. The first pathway begins with upregulation of the RAS, which in turn may activate the SNS. Altered autonomic tone may result in a wide range of systemic responses. As proof of this concept, animal toxicological evidence supports a direct link between the SNS and increased blood pressure following long-term $PM_{2.5}$ exposure. The second proposed pathway begins with pulmonary/systemic inflammation or olfactory transport of $PM_{2.5}$ and leads to neuroinflammation. Animal toxicological evidence supports a direct link between neuroinflammation and peripheral effects associated with metabolic syndrome and myocardial inflammation. In addition, neuroinflammation may lead to neurodegeneration and the development of Alzheimer's disease, as well as to impaired learning and memory and to behavioral issues. While experimental studies in animals contribute most of the evidence of upstream events, epidemiologic studies report associations between long-term exposure to $PM_{2.5}$ and reduced brain volume and cognitive impairment in adults. Neuroinflammation and neurodegeneration provide biological plausibility for epidemiologic results of increased hospital admissions or emergency department visits for Alzheimer's and Parkinson disease. In developing animals, neuroinflammation may potentially lead to neurodevelopmental disorders. These pathways will be used to inform a causality determination, which is discussed later in the chapter (Section 8.2.9).

8.2.2 Activation of the Sympathetic Nervous System and the Hypothalamic-Pituitary-Adrenal (HPA)Stress Axis

Activation of the SNS by long-term $PM_{2.5}$ exposure was investigated in animal toxicological studies (Table 8-8). Ying et al. (2014) evaluated the contribution of SNS to sustained increases in blood pressure, which have previously been observed in animals chronically exposed to $PM_{2.5}$. While studies have identified several mechanisms underlying this response, sympathetic activation had not been tested. C57BL/6J mice were exposed for 6 months to $PM_{2.5}$ CAPs in Columbus, OH. Exposure to $PM_{2.5}$ CAPs increased mean arterial blood pressure ($p < 0.05$), but did not affect heart rate or locomotor activity. Exposure to $PM_{2.5}$ CAPs also resulted in vascular dysfunction, which was measured ex vivo in terms of contractile response to phenylephrine and relaxation response to acetylcholine in mesenteric arteries (a type of resistance vessel) ($p < 0.05$). Two measures of sympathetic tone, low-frequency blood pressure variability and urinary norepinephrine excretion, were also increased in $PM_{2.5}$ CAPs-exposed mice ($p < 0.05$). Pharmacologic agents were used to test the role of the ANS in mediating responses to CAPs. Propranolol decreased heart rate in $PM_{2.5}$ CAPs exposed mice ($p < 0.05$), but not in controls. However, propranolol did not alter blood pressure in either group. Atropine had no effect on heart rate or blood pressure in either group. Acute inhibition of the central SNS with guanfacine resulted in a large decrease in blood pressure in both controls and $PM_{2.5}$ CAPs-exposed mice. This decrease was greater in $PM_{2.5}$ CAPs-exposed mice than in controls ($p < 0.05$). $PM_{2.5}$ CAPs exposure also increased the hypertensive response to air-jet stress ($p < 0.05$). Since sympathetic tone is modulated by hypothalamic inflammation in response to several pathophysiological signals, markers of hypothalamic inflammation were examined in $PM_{2.5}$ CAPs-exposed animals. Results, described in Section 8.2.3, provide evidence that $PM_{2.5}$ CAPs exposure mediates hypothalamic inflammation that may be linked to activation of the SNS and to an increase in sympathetic tone. Results of this study also indicate that increased sympathetic tone contributes to hypertension in response to $PM_{2.5}$ CAPs exposure.

Fonken et al. (2011) examined stress-related responses in C57BL/6J mice exposed for 10 months to $PM_{2.5}$ CAPs in Columbus, OH. No differences were found in serum corticosterone concentrations between control and $PM_{2.5}$-exposed mice, despite evidence of inflammation and morphological changes in the brain as described in Section 8.2.3 and Section 8.2.4.

In addition, the RAS may contribute to SNS activity. Long-term exposure to $PM_{2.5}$ CAPs resulted in upregulation of components of the RAS such as angiotensin I receptor and angiotensin converting enzyme in the heart, lung, and kidneys (Aztatzi-Aguilar et al., 2016; Aztatzi-Aguilar et al., 2015) (see Section 5.2.8, Section 6.2.7.2). Activity of the angiotensin converting enzyme results in angiotensin II formation from angiotensin I. Angiotensin II enhances the release of norepinephrine from sympathetic nerve endings via the angiotensin 1 receptor (Brasch et al., 1993). Sympathetic nerve activation, in turn, stimulates secretion of the angiotensin II precursor protein, renin, from the kidney, thus providing positive feedback for the pathway (Gordon et al., 1967).

Table 8-8 Study-specific details from animal toxicological studies of long-term exposure and activation of the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) stress axis.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Fonken et al. (2011) Species: mouse Strain: C57BL/6J Sex: male Age/Weight: 4 weeks	CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 94.4 µg/m^3 Duration: 6 h/day, 5 days/week for 10 mo Time to analysis: Behavioral testing occurred after approximately 9 mo Exposures were suspended for 3 weeks then resumed for 1 mo prior to tissue collection	Serum corticosterone
Ying et al. (2014) Species: mouse Strain: C57BL/6J Sex: male Age/Weight: 8 weeks	CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 107 µg/m^3 Duration: 6 h/day, 5 days/week for 6 mo	Sympathetic tone • urinary norepinephrine levels • low frequency variation of blood pressure Blood pressure Vascular dysfunction Heart rate Locomotion

CAPs = concentrated ambient particles; HEPA = high efficiency particulate absorber.

8.2.3 Brain Inflammation and Oxidative Stress

Recent experimental animal studies showing that long-term exposure to $PM_{2.5}$ CAPs can result in brain inflammation (Table 8-9) and oxidative stress add to the sparse evidence presented in the 2009 PM ISA. Several studies demonstrated that $PM_{2.5}$ CAPs exposure induced neuroinflammation and astrocyte activation in specific brain regions, as described below. Findings from these studies as they relate to neurodegeneration (Section 8.2.6), cognitive impairment, and behavioral effects (Section 8.2.5) are discussed in more detail in sections that follow.

Hippocampal inflammation was examined in several recent studies. Fonken et al. (2011) investigated the effects of a 10-month exposure to $PM_{2.5}$ CAPs from Columbus, OH on neuroinflammation and oxidative stress in the hippocampus of C57BL/6 mice. $PM_{2.5}$ CAPs exposure increased gene expression of proinflammatory cytokines TNFα and IL−1β ($p < 0.05$), but not of IL−6 and HMGB1. Upregulation of HO−1, a marker of oxidative stress ($p < 0.05$), was also seen, while the

microglial marker MAC1 was unchanged. Another study by the same group of investigators evaluated neuroinflammation in the hippocampus of $PM_{2.5}$ CAPs-exposed C3H/HeNHsd mice (Hogan et al., 2015). This mouse model is a nocturnal species with intact melatonin production. CAPs exposures for 4 weeks in Columbus, OH during a 14:10 light/dark cycle resulted in upregulation of IL−6 ($p < 0.05$), but not TNF or IL−1β. Tyler et al. (2016) exposed C67BL/6 and ApoE knockout mice to resuspended DEP for 30 days. In the hippocampus, there were increases in levels of mRNA for TGF-β in C67BL/6 mice ($p < 0.05$), but no changes in cytokine gene expression in ApoE knockout mice ($p < 0.05$). No inflammatory effects were seen in BALF although particle uptake into bronchial macrophages was increased in ApoE knockout, but not in C57BL/6 mice (see Section 5.2.9).

Ying et al. (2014) found evidence of hypothalamic inflammation in C57BL/6J mice exposed for 6 months to $PM_{2.5}$ CAPs from Columbus, OH. Increased hypothalamic gene expression of E-selectin, TNFα and ICAM−1 ($p < 0.05$) were observed. In addition, phosphorylation of IKK was increased in the arcuate nucleus but not in the paraventricular nucleus of the hypothalamus, while the number of c-fos positive cells was increased in both ($p < 0.05$). These results indicate activation of the NFκB pathway and upregulation of pro-inflammatory genes as a result of exposure to $PM_{2.5}$ CAPs. Hypothalamic inflammation was also demonstrated in Liu et al. (2014), in a genetically susceptible model of Type II diabetes, the KKay mouse, following exposure to $PM_{2.5}$ CAPs from Columbus, OH for 5−8 weeks. Increased gene expression of IL−6, TNFα, and IKKβ was observed ($p < 0.05$). In addition, the amount of oxidized phospholipid Ox-PAPC, which can activate TLR pathways, was increased in brain tissue. TLR pathways are involved in activation of the innate immune system. Subsequently, mice were treated with an inhibitor of IKKβ, which blocks NFκB activation, by inter-cerebroventricular infusion during a 4-week exposure to $PM_{2.5}$ CAPs. Central IKKβ inhibition dampened the effects of CAPs exposure on hypothalamic inflammation, including IL−6 and IKKβ gene expression and activation of microglia and astrocytes, as indicated by IBA−1 and GFAP immunostaining, respectively ($p < 0.05$). Exposure to $PM_{2.5}$ CAPs enhanced hyperglycemia, insulin resistance, and peripheral inflammation (see Section 7.2.3.2) that was dampened by IKKβ inhibition. Liu et al. (2014) provides evidence that the central nervous system, possibly via hypothalamic inflammation, contributes to the diabetic phenotype in CAPs-exposed susceptible mice. Treatment with this same inhibitor of IKKβ by intra-cerebroventricular infusion blocked myocardial inflammation in a separate study of long-term $PM_{2.5}$ CAPs exposure in KKay mice (Zhao et al., 2015). Evidence of hypothalamic inflammation was also found in spontaneously hypertensive (SH) rats exposed to CAPs from Columbus, OH for 15 weeks (Ying et al., 2015). Expression of TNFα mRNA in the hypothalamus was increased ($p < 0.05$) and returned to baseline 5 weeks following the end of exposure.

Bhatt et al. (2015) investigated the effects of $PM_{2.5}$ CAPs exposure on brain inflammation and markers of Alzheimer's disease in C57BL/6 mice. Exposure to $PM_{2.5}$ CAPs from Columbus, OH for 9 months, but not 3 months, resulted in increases in several indices of inflammation and early Alzheimer's disease-related pathology in the temporal cortex. This included a subset of cytokines, COX−1 and COX−2, PSD−95, and amyloidβ 1−40 ($p < 0.05$). A decrease in amyloid precursor protein

(APP) levels was observed, along with an increase in the beta-site APP cleaving enzyme (BACE) ($p < 0.05$). No changes in tau, synaptophysin, markers of oxidative stress, DNA methylation or activation of astrocytes (GFAP), glia (1BA−1), or endothelial cells (VCAM−1) were found.

However, changes in gene expression were not found in every study involving $PM_{2.5}$ CAPs. Ljubimova et al. (2013) examined changes in global gene expression in the brain, as well as expression of Arc and Rac genes and their protein products, in Fischer 344 rats exposed to $PM_{2.5}$ CAPs in Riverside, CA for 10 months. Exposure did not induce changes in gene or protein expression in this study.

In summary, inflammation was observed in the hippocampus, hypothalamus, and temporal cortex of several different mice strains exposed for 1−10 months to $PM_{2.5}$ CAPs. Hippocampal inflammation, in the absence of pulmonary inflammation, was also found in mice exposed to traffic-related $PM_{2.5}$. In a mouse model of diabetes, $PM_{2.5}$ CAPs-exposure induced hypothalamic inflammation that was linked to a worsening of the diabetic phenotype and to myocardial inflammation. Hypothalamic inflammation was found to be reversible with cessation of exposure in SH rats. In the temporal cortex, brain inflammation was observed in conjunction with markers of Alzheimer's disease following $PM_{2.5}$ CAPs exposure. Oxidative stress was also seen in the hippocampus and hypothalamus.

Table 8-9 Study-specific details from animal toxicological studies of long-term exposure to $PM_{2.5}$ and brain inflammation and oxidative stress.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Bhatt et al. (2015) Species: mouse Sex: male Strain: C57BL/6 Age/Weight: 8 weeks	CAPs from Columbus, OH Particle size: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 65.7 ± 354.2 µg/m^3 Duration: 6 h/day, 5 days/week for 3 or 9 mo	Immunoassays of temporal cortex • cytokines • COX−1, COX−2 • Markers of oxidative stress 3NT, HNE-adducts • Markers of astrocyte (GFAP), glial (IBA−1) or vascular (VCAM−1) activation • Markers of Alzheimer's disease: Aβ, tau, APP and cleaving enzyme BACE • Postsynaptic marker PSD−95 • DNA methylation

Table 8-9 (Continued): Study-specific details from animal toxicological studies of long-term exposure to $PM_{2.5}$ and brain inflammation and oxidative stress.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Fonken et al. (2011) Species: mouse Strain: C57BL/6J Sex: male Age/Weight: 4 weeks	CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 94.4 µg/m^3 Duration: 6 h/day, 5 days/week for 10 mo Time to analysis: Exposures were suspended for 3 weeks then resumed for 1 mo prior to tissue collection	Brain tissue—hippocampus • morphology • gene expression
Hogan et al. (2015) Species: mouse Strain: C3H/HeNHsd Sex: male Age/Weight: 8 weeks	CAPs from Columbus, OH Particle Sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 94.4 µg/m^3 Duration: 6 h/day, 5 days/week for 4 weeks Time to Analysis: Exposures were suspended for 3 weeks then resumed for 1 mo prior to tissue collection	Brain tissue—hippocampus • morphology • gene expression
Liu et al. (2014) Species: mouse Strain: KKay Sex: Age/Weight: 5–7 weeks	CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: filtered air	Route: Whole body inhalation Dose/Concentration: 107 µg/m^3 Duration: 6 h/day, 5 days/week for 4, 5 or 8 weeks	Hypothalamic tissue: Gene expression and immunostaining—inflammatory markers in hypothalamus Brain tissue: LC/MS— Oxidized phospholipids Glucose homeostasis Insulin sensitivity Oxygen consumption Heat production Blood and peripheral tissues: Markers of inflammation
Ljubimova et al. (2013) Species: Rat Sex: Male Strain: Fisher 344 Age/Weight: 3–7 weeks	CAPs from Riverside, CA (summer) Particle size: 0.18–2.5 µm Control: Filtered air	Route: Whole body inhalation Dose/Concentration: 149 ± 24 µg/m^3 67 ± 6 particles/cm^3 10–3 Duration: 5 h/day, 4 days/week for 1, 3, and 10 mo	Brain tissue—Immunohistochemistry Gene expression—mRNA

Table 8-9 (Continued): Study-specific details from animal toxicological studies of long-term exposure to $PM_{2.5}$ and brain inflammation and oxidative stress.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Tyler et al. (2016) Species: Mouse Strain: C57BL/6 and ApoE knockout Age/Weight: 6–8 weeks	DEP, resuspended Particle size: 1.5–3.0 μM ± 1.3–1.6 μM Control: filtered air	Route: Whole body inhalation Dose/Concentration: 315.3 ± 50.7 μg/m^3 Duration: 6 h/d for 30 days	Hippocampus tissue: Cytokine gene expression
Ying et al. (2014) Species: mouse Strain: C57BL/6J Sex: male Age/Weight: 8 weeks	CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 107 μg/m^3 Duration: 6 h/day, 5 days/week for 6 mo	Brain tissue: Gene expression—inflammatory markers in hypothalamus
Ying et al. (2015) Species: Rat Strain: SHR Sex: Male Age/Weight: 5 weeks	CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: filtered air	Route: Whole body inhalation Dose/Concentration: 128.3 ± 60.4 μg/m^3 Duration: 6 h/day, 5 days/week for 15 weeks Time to analysis: immediately or 5 weeks later	Gene expression—inflammatory markers In hypothalamic, lung, heart tissue

3–NT = 3–nitrotyrosine; Aβ = amyloid beta; ApoE = apolipoprotein E; APP = amyloid precursor protein; BACE = beta-secretase 1; CAPs = concentrated ambient particles; COX = cyclooxygenase; GFAP = glial fibrillary acidic protein; HEPA = high efficiency particulate absorber; HNE = hydroxynonenol; IBA–1 = ionized calcium binding adaptor molecule; LC/MS = liquid chromatography/mass spectrometry, PSD = postsynaptic density protein; VCAM = vascular cell adhesion molecule.

8.2.4 Morphologic Changes in the Brain

There were no epidemiologic studies relating long-term exposure to $PM_{2.5}$ to changes in brain morphology evaluated in the 2009 PM ISA. However, an animal toxicological study found Parkinson disease-like brain histopathology following long-term exposure to $PM_{2.5}$ CAPs in ApoE knockout mice (Veronesi et al., 2005). Dopaminergic neurons were decreased in substantia nigra, which is part of the midbrain, and GFAP immunoreactivity, an indicator of astrocyte activation, was increased in the nucleus compacta, which is part of the substantia nigra.

Recent analyses from two established cohorts (Casanova et al., 2016; Chen et al., 2015; Wilker et al., 2015), using magnetic resonance imaging (MRI) to identify attributes or changes in brain structure that may stem from neurodegenerative processes or cerebrovascular dysfunction, report $PM_{2.5}$ associated reductions in brain volume (Table 8-910). Morphologic changes in the brain were also demonstrated in experimental animal studies (Table 8-11). These changes were accompanied by inflammation (Section 8.2.3).

Epidemiologic Studies

The effect of long-term exposure to $PM_{2.5}$ on brain morphology, using MRI scans, was studied in older women (age 65–80) who were free of dementia at baseline when they were enrolled in the Women's Health Initiative Memory Study (WHIMS) (Chen et al., 2015). Information on a wide array of covariates including individual characteristics such as hormone replacement therapy, BMI, lifestyle, depression, cardiovascular risk factors and SES was collected for WHIMS. A pattern of lower white matter (WM) volume of the frontal, parietal and temporal areas of the brain in fully adjusted models with increasing cumulative $PM_{2.5}$ exposures was observed [−8.30 cm^3 (95% CI: −4.70, −11.89) decrease in total WM]. Details on the quantitative relationship between $PM_{2.5}$ and gray matter (GM) were not reported because they did not reach statistical significance. This research was extended through the analyses conducted by Casanova et al. (2016) using finely grained voxel-wise methods, which are better able to detect patterns that extend across multiple brain regions. Increased 3-year average $PM_{2.5}$ concentrations was associated with smaller subcortical WM and smaller cortical GM volumes in the multi-variable models used in this study. The exposure metrics (3 year average and cumulative average) used in WHIMS analysis were highly correlated ($r = 0.93$).

In a cross-sectional analysis of the Framingham Heart Offspring Study, Wilker et al. (2015) examined the association of long-term $PM_{2.5}$ exposure with total cerebral brain volume, hippocampal volume, WM hyperintensity volume, and preclinical brain infarcts among older men and women (≥60 years old) who were free of dementia and stroke. Wilker et al. (2015) reported that total cerebral brain volume was smaller with increasing $PM_{2.5}$ exposure after adjustment for covariates [−0.80 cm^3 (95% CI: −0.13, −1.48) total cerebral brain volume]. After further adjustment for risk factors for cardiovascular disease, this association persisted but lost precision. An increased risk of covert brain infarcts was also observed [OR: 2.58 (95%CI: 1.27, 5.24)].

Table 8-10 Epidemiologic studies examining the association between long-term $PM_{2.5}$ exposures and brain morphology using magnetic resonance imaging (MRI).

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†(Chen et al., 2015) 2 RCTs, U.S. $PM_{2.5}$: 1999–2006 Outcome: 2005–2006	WHIMS n = 1,403	Cumulative avg for geocoded residential history, BME-based spatiotemporal model, C-V R2 = 0.9	Median: 12.24 IQR: 10.67–14.16	GM, WM volumes	Correlations (r): NR Copollutant models: NR
†(Casanova et al., 2016) $PM_{2.5}$: 1999–2010 Outcome: 1996/98–2005–2006	WHIMS N = 1,365	3-yr avg at residence, BME spatio-temporal model to estimate C-V R2 = 0.74	NR	GM, WM, hippocampal volumes	Correlations (r): NR Copollutant models: NR
†(Wilker et al., 2015) Cross-sectional $PM_{2.5}$: 2000 Outcome: 1998–2001	Framingham Offspring Study N = 943	Satellite derived AOD with LUR, see (Kloog et al., 2012)	Median = 11.1 IQR = 1.7	Hippocampal volume, WM hyper-intensity volume Total cerebral brain volume	Correlations (r): NR Copollutant models: NR

BME = Bayesian Maximum Entropy; C-V = cross validation; GM = grey matter; LUR = land use regression; MRI = Magnetic Resonance Imaging; NR = Not Reported; RCT = Randomized Clinical Trial; WHIMS = Women's Health Initiative Memory Study; WM = white matter; y=year(s).

†Studies published since the 2009 PM ISA.

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Animal Toxicological Studies

Fonken et al. (2011) investigated morphologic changes in the hippocampus of C57BL/6 mice exposed for 10 months to $PM_{2.5}$ CAPs from Columbus, OH. $PM_{2.5}$ CAPs exposure resulted in structural changes in the hippocampus. Apical spine density in the CA1 region of the hippocampus was decreased ($p < 0.05$). Basilar spine density in the CA1 region and spine density in the CA3 and dentate gyrus (DG) regions were unchanged. Apical dendritic length and cell complexity were also decreased by $PM_{2.5}$ CAPs exposure ($p < 0.05$), although cell body area was unchanged. Another study by the same group of investigators found altered brain morphology in C3H/HeNHsd mice exposed for 4 weeks to $PM_{2.5}$ CAPs during a 14:10 light/dark cycle (Hogan et al., 2015). This mouse model is a nocturnal species with intact melatonin production. $PM_{2.5}$ CAPs exposures resulted in decreased apical and basilar spine densities, apical dendritic length, and cell body area in the CA1 region of the hippocampus ($p < 0.05$).

Table 8-11 Study-specific details from animal toxicological studies of long-term $PM_{2.5}$ exposure and morphologic effects.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Fonken et al. (2011) Species: mouse Strain: C57BL/6J Sex: male Age/Weight: 4 weeks	CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 94.4 µg/m^3 Duration: 6 h/day, 5 days/week for 10 mo Time to analysis: Exposures were suspended for 3 weeks then resumed for 1 mo prior to tissue collection	Brain tissue—hippocampus • morphology
Hogan et al. (2015) Species: mouse Strain: C3H/HeNHsd Sex: male Age/Weight: 8 weeks	CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 94.4 µg/m^3 Duration: 6 h/day, 5 days/week for 4 weeks Time to analysis: Exposures were suspended for 3 weeks then resumed for 1 mo prior to tissue collection	Brain tissue—hippocampus • morphology

CAPs = concentrated ambient particles; HEPA = high efficiency particulate absorber; mo=month(s).

8.2.5 Cognitive and Behavioral Effects

8.2.5.1 Animal Toxicological Studies

Fonken et al. (2011) investigated affective and cognitive processes in C57BL/6 mice exposed for 10 months to $PM_{2.5}$ CAPs in Columbus, OH (Table 8-12). Behavioral testing showed that $PM_{2.5}$ CAPs exposure had a number of effects – impaired spatial learning and spatial memory, as measured in the Barnes maze ($p < 0.05$); increased behavioral despair and a more rapid onset of behavioral despair as measured in the Porsolt forced swim test ($p < 0.05$); and increased anxiety-like behavior in one of two tasks (time spent in the center of an open field, $p < 0.05$). Neuroinflammation and morphologic changes, described in Section 8-26 and Section 8-30, may be related to changes in cognition and affective processes. Another study by the same group of investigators examined affective and cognitive processes in C3H/HeNHsd mice exposed for 4 weeks to $PM_{2.5}$ CAPs during a 14:10 light/dark cycle (Hogan et al., 2015). This mouse model is a nocturnal species with intact melatonin production. Behavioral testing demonstrated an effect of CAPs exposure on locomotion and anxiety-like responses (time spent in the center of an open field, $p < 0.05$), but no effects on depressive responses.

Table 8-12 Study-specific details from animal toxicological studies of long-term $PM_{2.5}$ exposure and cognitive and behavioral effects.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Fonken et al. (2011) Species: mouse Strain: C57BL/6J Sex: male Age/Weight: 4 weeks	CAPs from Columbus, OH Particle Sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 94.4 µg/m^3 Duration: 6 h/day, 5 days/week for 10 mo Time to analysis: Behavioral testing occurred after approximately 9 mo. Exposures were suspended for 3 weeks then resumed for 1 mo prior to tissue collection	Behavioral testing Physical measurements Locomotor behavior and anxiety-like responses Cognitive processes—learning and memory

Table 8-12 (Continued): Study-specific details from animal toxicological studies of long-term $PM_{2.5}$ exposure and cognitive and behavioral effects.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Hogan et al. (2015) Species: mouse Strain: C3H/HeNHsd Sex: male Age/Weight: 8 weeks	CAPs from Columbus, OH Particle Sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 94.4 μg/m^3 Duration: 6 h/day, 5 days/week for 4 weeks Time to analysis: Behavioral testing occurred after approximately 9 mo. Exposures were suspended for 3 weeks then resumed for 1 mo prior to tissue collection	Behavioral testing • locomotor behavior • anxiety-like responses • depressive-like responses

CAPs = concentrated ambient particulates; HEPA = high efficiency particulate absorber.

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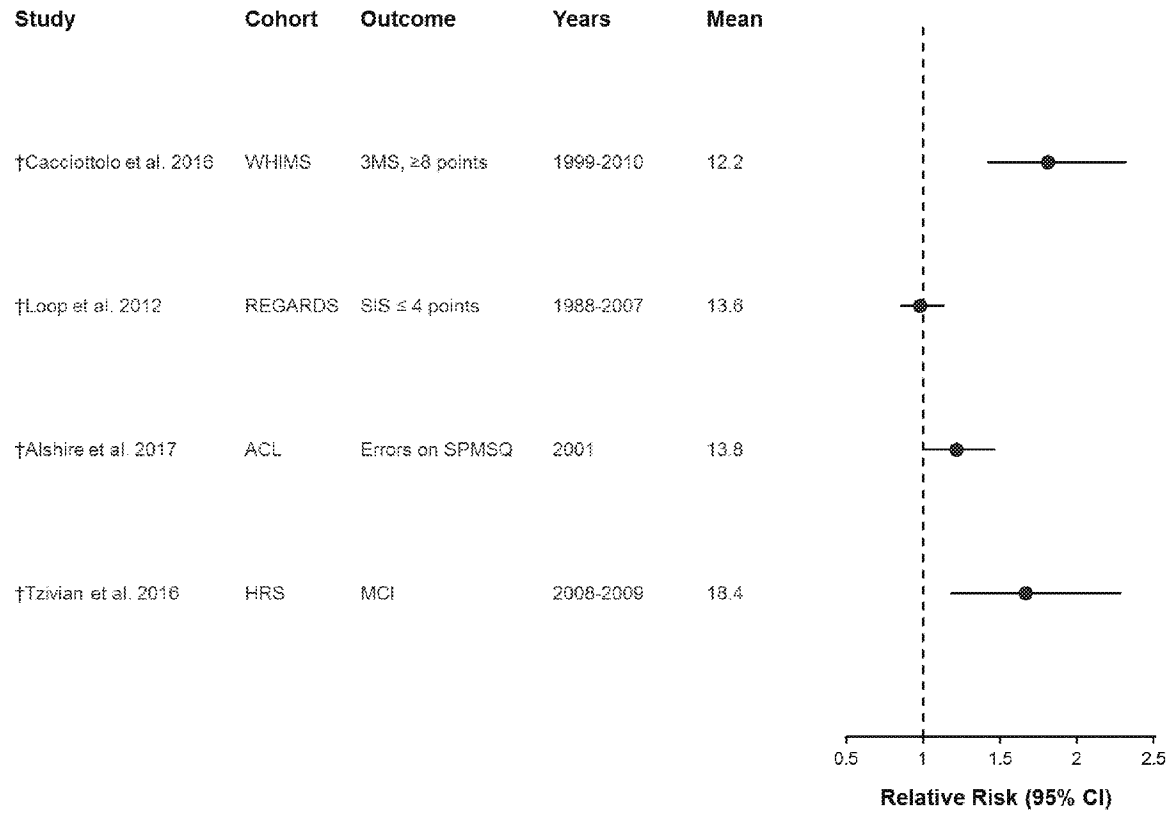
8.2.5.2 Epidemiologic Studies

2 Although there were no studies of long-term exposure to $PM_{2.5}$ evaluated in the 2009 PM ISA
3 (U.S. EPA, 2009), Chen and Schwartz (2009) reported a cross-sectional association of annual average
4 exposure to PM_{10} with cognitive function using data from NHANES III. Multiple additional studies
5 reporting associations with dichotomous measures of cognitive function or effects on continuous
6 measures of global or domain specific subtests of cognitive function add to the evidence in the current
7 review. Overall, these studies were heterogeneous in their methods and design, and their findings were
8 not entirely consistent. Several high-quality studies reported associations with long-term exposure to
9 $PM_{2.5}$, however.

10 Studies that modeled cognitive decline as a dichotomous outcome are presented in Figure 8-3.
11 Cacciottolo et al. (2017) examined the effect of long-term $PM_{2.5}$ exposure on accelerated global cognitive
12 decline among WHIMS participants using a cutpoint of ≥8 points on the Modified Mini-Mental State
13 (3MS). The authors report an increased risk of accelerated global cognitive decline in adjusted models
14 [HR: 1.81 (95%CI: 1.42, 2.32) comparing 3-year moving average concentration >12 to ≤12 μg/m^3] in the
15 women, with a larger HR among carriers of the APOE allele Ɛ4/4. Cacciottolo et al. (2017) considered
16 potential confounders including age, geographic region, education income, employment, lifestyle factors,
17 and clinical characteristics (i.e., hormone treatment, depression, BMI, hypercholesterolemia,
18 hypertension, diabetes, history of CVD) in their analysis. In a study of the effect of $PM_{2.5}$ on pre-clinical
19 cognitive impairment, Loop et al. (2013) analyzed data from a large U.S. cohort designed to study stroke
20 (REGARDS). Authors conducted a cross-sectional analysis of incident cognitive impairment using
21 logistic regression and adjusting for length of follow-up. $PM_{2.5}$ exposure was not associated with

cognitive impairment, defined as a score of ≤4 on a telephone administered Six-Item Screener (SIS), after full adjustment for potential confounders including demographic factors and incident stroke. Ailshire et al. (2017) analyzed U.S. national scale data from the Americans Changing Lives (ACL) survey reporting and increased error rate on the Short Portable Mental Status Questionnaire (SPMSQ) in association with $PM_{2.5}$ exposure that was worse in areas of high neighborhood stress. Tzivian et al. (2016) reported a positive association between long-term $PM_{2.5}$ exposure and prevalence of mild cognitive impairment (MCI) in the HRS study [OR: 1.67 (95%CI: 1.18, 2.29)] that remained after adjustment for noise. MCI was defined to identify cases with subjective cognitive complaints and objective impairment that did not reach the criteria for dementia.



Circles represent beta coefficients; horizontal lines represent 95% confidence intervals. Red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Concentrations are in $\mu g/m^3$. Results are standardized to a 5 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table S8-1 (U.S. EPA, 2018).

3MS = Modified Mini-Mental State; ACL = Americans Changing Lives; HRS = Health and Retirement Survey; REGARDS = Reasons for Geographic and Racial Differences in Stroke; SIS = Six-Item Screener; SPMSQ = Short Portable Mental Status Questionnaire; WHIMS = Women's Health Initiative Memory Study.

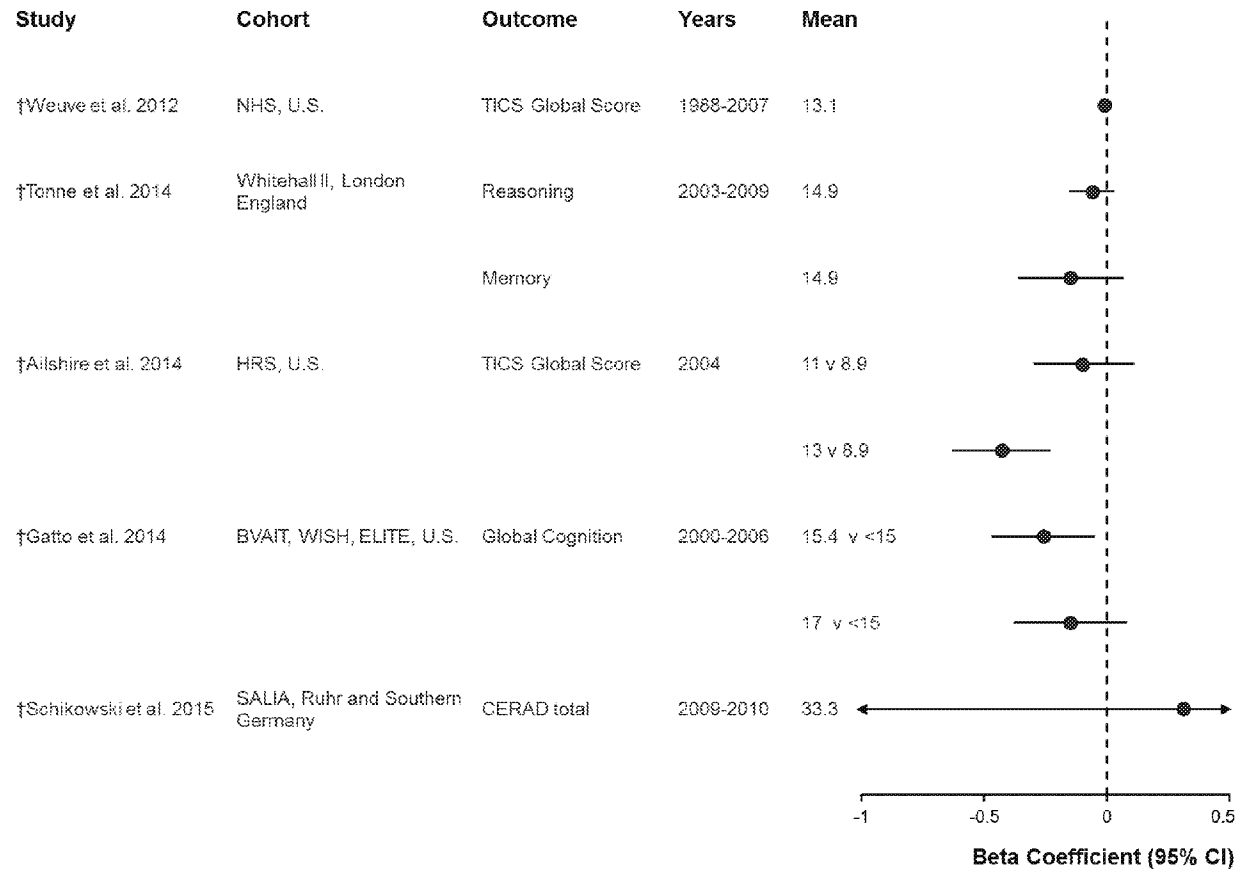
†Studies published since the 2009 PM ISA.

Figure 8-3 Associations between long-term exposure to $PM_{2.5}$ and cognitive effects. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration (unless otherwise noted).

Small changes on cognitive test scores were observed in some but not all studies that evaluated these changes using continuous variables (Table 8-123, Figure 8-4). Weuve et al. (2012) measured the change in cognitive function of women enrolled in the Nurses' Health Study (NHS) with no history of stroke, using the validated Telephone Interview for Cognitive Status (TICS) instrument. Investigators used month-long average $PM_{2.5}$ concentrations to compute metrics indicating $PM_{2.5}$ exposures for several highly correlated time periods prior to the cognitive function assessment. Results for the longest duration

multi-year exposure metric are included in Figure 8-4. $PM_{2.5}$ was associated with a small decrease in global cognitive test score during the 2-year period between successive outcome measurements ($\beta = -0.01$ (95%CI: −0.02, 0.00) that is approximately equivalent to a decrease expected with 1 year of aging. This association persisted after adjustment for potential confounders including SES and cardiovascular conditions (i.e., high blood pressure, CHD, CHF, coronary artery bypass graft, TIA, and carotid endarterectomy). Tonne et al. (2014) used a set of tests designed to measure reasoning, memory, semantic fluency, and phonemic fluency to examine the association with long-term exposure to $PM_{2.5}$. Only associations with 5-year average concentrations are presented in Figure 8-4 because results were generally similar across exposure metrics. Authors reported 5-year declines on several cognitive tests [e.g., Reasoning: −0.06 (95% CI: −0.15, 0.03) and Memory: −0.15 (95% CI: −0.36, 0.07)].

Several cross-sectional analyses were also conducted. Ailshire and Crimmins (2014) used the TICS instrument to assess the cross-sectional association of annual average $PM_{2.5}$ concentration with cognitive effects reporting associations comparing the upper and third quartiles of exposure to the reference category (8.9 $\mu g/m^3$). The component of the TICS score reflecting episodic memory, rather than mental status, appeared to drive the observed association. In a cross-sectional analysis of several clinical trial participants enrolled through the University of Southern California, Gatto et al. (2014) found small decreases in global cognition, as well as decreases in several domain-specific tests that comprised a global cognition score. In the SALIA cohort, Schikowski et al. (2015) examined the association of $PM_{2.5}$ exposure with several domain-specific tests of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery, which includes the Mini Mental State Examination (MMSE). Although no association of $PM_{2.5}$ with global cognition was observed, associations with a figure copying subtest measuring constructional praxis was reported (ten subtests were administered).



Note: Ailshire and Crimmins (2014) and Gatto et al. (2014) specify exposure categories and compare the categories to a reference group (8.9 μg/m$_3$). Circles represent beta coefficients; horizontal lines represent 95% confidence intervals. Red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Concentrations are in μg/m^3. Results are standardized to a 5 μg/m^3 increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table S8-2 (U.S. EPA, 2018).

BVAIT = B-Vitamin Atherosclerosis Intervention Trial, ELITE = Early versus Late Intervention Trial with Estradiol, CERAD = Consortium to Establish a Registry for Alzheimer's Disease, HRS = Health and Retirement Study, NHS=Nurses' Health Study, SALIA = Study of the Influence of Air Pollution on Lung Function, TICS = Telephone Interview for Cognitive Status, Whitehall II=Study of British Civil Servants, v = versus; WISH = Women's Isoflavone Soy Health.

†Studies published since the 2009 PM ISA.

Figure 8-4 Associations between long-term exposure to $PM_{2.5}$ and cognitive effects. Associations are presented per 5 μg/m^3 increase in pollutant concentration (unless otherwise noted).

Table 8-13 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and cognitive function.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Cacciottolo et al. (2017) Prospective cohort $PM_{2.5}$: 1999–2010 Outcome: 1995/99–2010	WHIMS n = 3,467 women (65–79 yr) w/specific APOE alleles	3-yr moving avg for geocoded residential history, BME-based spatiotemporal model, C-V R2 = 0.7	Median: 12.24 IQR: 10.67–14.16	Accelerated cognitive decline (≥8 point loss on 3MS) and dementia (determined by central adjudication) Interaction with APOE alleles	Correlations (r): NR Copollutant models: NR
†Loop et al. (2013) 48 contiguous US states Prospective cohort $PM_{2.5}$: 2003–2009 Outcome: 2003/07–2009	REGARDS (mean age 64 yr) N = 20,150	1 yr avg (prior to baseline), AOD plus monitors, 10 × 10 km grid, see (Al-Hamdan et al., 2014)	Median: 13.6 IQR: 12.2–14.8	SIS score ≤4	Correlations (r): NR Copollutant models: NR
†Tzivian et al. (2016) German Ruhr area Cross-sectional $PM_{2.5}$: 2008–2009 Outcome: 2006/2008	HNR study N = 4,086 50–80 yr	Annual avg at residential address, LUR, R2 comparing modelled and measured $PM_{2.5}$ = 0.88	Mean: 18.39 (SD: 1.05) IQR: 1.4	MCI (Petersen/International Working group on MCI criteria) (Petersen, 2004)	Correlations (r): NR Copollutant models: NR
†Weuve et al. (2012) 11 US states Longitudinal Cohort $PM_{2.5}$: 1988–2007	NHS Women ≥70 yr N = 19,409	1 mo, 1 yr, 2 yr, 5 yr avg prior to baseline assessment. Pre- and post–1999	5 yr Avg: 8.5	TICS Global score	$PM_{10-2.5}$ R = 0.1–0.22 depending on metric (*r* across averaging times of each size fraction 0.97–0.98)
†Tonne et al. (2014) greater London Longitudinal Cohort $PM_{2.5}$ 2003–2009 Outcome: 2007/2009	Whitehall II (mean 66 yr) N = 2,867	Annual avg, 1 yr lag 4, 3 yr avg, 5 yr avg, dispersion model, *r* = 0.74 (2008, 15 monitors)	5 yr Avg: 14.9 IQR: 0.25	Cognitive test performance 5 yr decline	$PM_{2.5}$ exhaust

Table 8-13 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and cognitive function.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Ailshire and Crimmins (2014) Cross-sectional US National Survey 2004	HRS N = 13,996 ≥50 yr	Annual avg (2004), within 60 km census tract centroid for residence	Median: 12.2 IQR: 3.9	Episodic memory and mental status TICs	Correlations (r): NR Copollutant models: NR
†Ailshire et al. (2017) U.S. National Survey $PM_{2.5}$ = 2001 Outcome: 2001/2002	ACL N = 79 ≥55 yr	Annual avg, within 60 km of census tract centroid	Mean (SD) 13.78 (3.13)	Rate of incorrect response on SPMSQ	Correlations (r): NR Copollutant models: NR
†Gatto et al. (2014) Los Angeles Cross-sectional 2000–2006	BVAIT, WISH, ELITE (mean age 60.5 yr) N = 1,496	1 yr avg for year of randomization at residence, IDW interpolation of monitor concentration (within 5 km or avg of 3 monitors within 100 km) See (Peters et al., 2004)	NR	14 cognitive tests and global score	Copollutant correlations (r): Ozone (r = 0.62), NO_2 (r = 0.8)
†Schikowski et al. (2015) Ruhr and Southern Muensterland, Germany Cross-sectional Outcome 2007–2009 $PM_{2.5}$: 2009–10 Back-extrapolation: 1985/1995 (baseline exam)	SALIA Women (mean 73.4 yr) N = 789	Multi-yr avg, LUR with back extrapolation, see (Eeftens et al., 2012a) Mean model explained variance R2 = 0.71 (range: 0.32–0.81) C-R R2 8–11% lower	Median 33.3 and IQR 4.7 at baseline (1995) Median 17.4 and IQR 1.8 at follow-up (2007)	Global Cognition (MMSE and CERAD) Fig-C Modification by APOE allele	Correlations (r): NR Copollutant models: NR

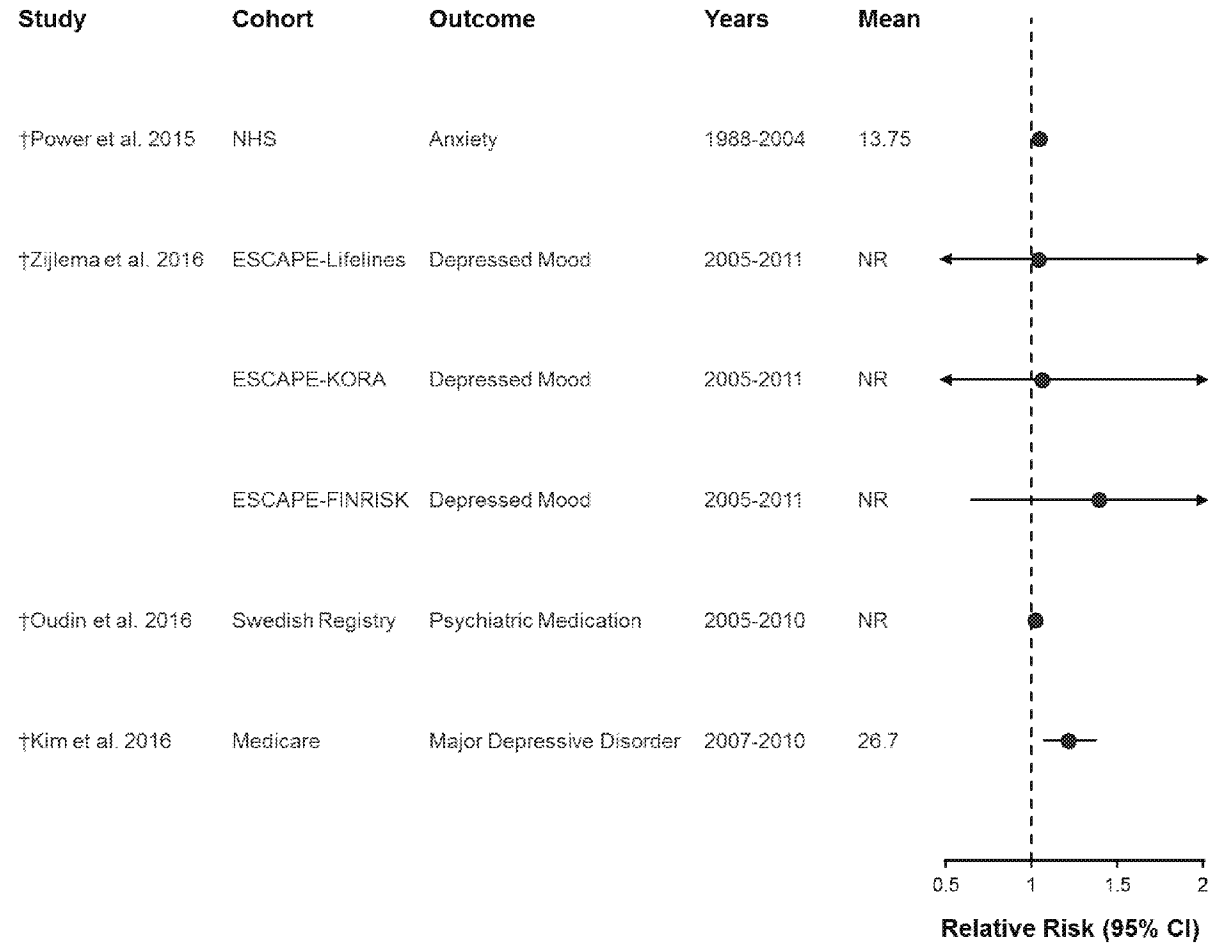
ACL = Americans' Changing Lives; BVAIT = B-Vitamin Atherosclerosis Intervention Trial; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; ELITE = Early versus Late Intervention Trial with Estradiol; BMI = Body Mass Index; HRS = Health and Retirement Study; MCI = Mild Cognitive Impairment; NHS = Nurses Health Study; RCT = Randomized Controlled Trial; REGARDS = Reasons for Geographic and Racial Differences in Stroke; SALIA = Study of the Influence of Air Pollution on Lung Function, Inflammation, and Aging; SIS = Six-Item Screener (cognitive function); SPMSQ = Short Portable Mental Status Questionnaire; TICS = Telephone interview for Cognitive Status; WISH = Women's Isoflavone Soy Health.

†Studies published since the 2009 PM ISA.

Anxiety and Depression

There were no analyses of the association of long-term exposure to $PM_{2.5}$ with anxiety or depression evaluated in the 2009 PM ISA. Several studies are currently available that examine associations with depressive, anxiety, or use of psychiatric medication (Figure 8-5, Table 8-14). Overall, these studies do not report consistently positive associations and the magnitude of the association varies substantially by study. Within the European ESCAPE project, statistical evidence of heterogeneity across cohorts was observed, precluding meta-analysis of cohort-specific results.

Power et al. (2015) analyzed data from the NHS to determine the association between several exposure metrics averaged from 1 month to multiple years (1988–2004) and anxiety among older women. Authors observed positive associations between prevalent anxiety and multi-year average concentration [OR: 1.04 (95% CI: 1.00, 1.09)]. The associations with shorter averaging times were also present [e.g., 1.06 (95% CI: 1.03, 1.09) per 5 $\mu g/m^3$ increase in 1-mo avg concentration], and models that adjusted for averaging time indicated the strongest associations were with shorter averaging times. In a cross-sectional analysis of ESCAPE, Zijlema et al. (2015) observed heterogenous results across cohorts with a large imprecise positive association among FINRISK participants [OR: 1.39 (95% CI: 0.64, 3.05)] and associations that were close to the null in other cohorts. In a longitudinal analysis of use of psychiatric medication reported in the national registry of Sweden, (Oudin et al., 2016) reported a small positive association between use of psychiatric medication and PM_{10} [1.02 (95% CI: 1.00, 1.04)], noting that the association was similar to the association with $PM_{2.5}$. A relatively large association with major depressive disorder was reported by Kim et al. (2016) in an analysis of the National Health Insurance Database (NHID) of Korea [HR: 1.21 (95% CI: 1.07, 1.38)], where the annual average $PM_{2.5}$ concentration was 26.7 $\mu g/m^3$.



Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in $\mu g/m^3$. Hazard Ratios are standardized to a 5 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table S8-3 (U.S. EPA, 2018).

ESCAPE = European Study of Cohorts for Air Pollution Effects; FINRISK = Finland Risk; KORA = Kooperative Gesundheitsforschung in der Region Augsburg; NHS = Nurses' Health Study; NR = Not Reported.

†Studies published since the 2009 PM ISA.

Figure 8-5 Associations between long-term exposure to $PM_{2.5}$ and indicators of depression or anxiety. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration.

Table 8-14 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and indicators of depression or anxiety.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Power et al. (2015) $PM_{2.5}$: 1988–2004 Outcome: 2004	NHS N = 71,271 Mean age 70 yr	Multi-year, annual avg, 1 mo, 3 mo and 6 mo prior to outcome, spatio-temporal, at residence (pre-1999 $PM_{2.5}$ estimated from PM_{10} ratio)	Mean (SD): 1 mo = 12.74 (4.18); 3 mo = 12.13 (3.4), 6 mo = 11.59 (2.60); 12 mo = 11.38 (2.60); 1988–2003 = 13.75 (2.82)	Crown-Crisp phobic anxiety scale score ≥6 (prevalent)	$PM_{10-2.5}$ Correlations (r): 0.24 Copollutant model: NR
†Zijlema et al. (2015) Cross-sectional $PM_{2.5}$ ESCAPE: 2008–2011 $PM_{2.5}$ EU-wide protocols: 2005–2007	ESCAPE plus LifeLines N = 70,928	LUR, at residence using ESCAPE and EU-wide protocols incorporating satellite derived AOD. (Vienneau et al., 2013; Eeftens et al., 2012b)	Lifelines (highest): Median 15.4 IQR 0.16	Depressed mood, questionnaire or interview	ESCAPE correlations (r): 0.44–0.53 NO_2 EU-wide correlations (r): 0.33–0.53
†(Oudin et al., 2016) Longitudinal 4 counties, Sweden $PM_{2.5}$: 2005–2010 Outcome: 2005–2010	Swedish National Register N = 552,221	Annual avg for year of inclusion, LUR (estimated from ratio with PM_{10}), resolution of 1 km; C-V R2 PM_{10} = 0.85–0.95	NR	Medication for psychiatric disorders	Correlations (r): NR Copollutant models: NR Note: PM_{10} results presented because they were similar to $PM_{2.5}$ results
†Kim et al. (2016) Seoul, South Korea Longitudinal $PM_{2.5}$: 2007–2010 Outcome: 2008–2010	NHID N = 27,270	1 yr moving avg, 27 monitors	26.7 Range across districts 2007: 19.8–27.4	Major depressive disorder (ICD10 F32.x, F33.x, F34.1, F41.2)	Correlations (r): NR Copollutant models: NR

AOD = Aerosol Optical Depth; CESD-R = Center for Epidemiologic Studies Depression Scale-Revised; ESCAPE = European Study of Cohorts for Air Pollution Effects; IQR = Inter-quartile Range; LUR = land use regression; MOBILIZE = Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston; NHID = National Health Insurance Database; N, n = number of subjects; NR = Not Reported; SD = Standard Deviation; yr = year(s).

†Studies published since the 2009 PM ISA.

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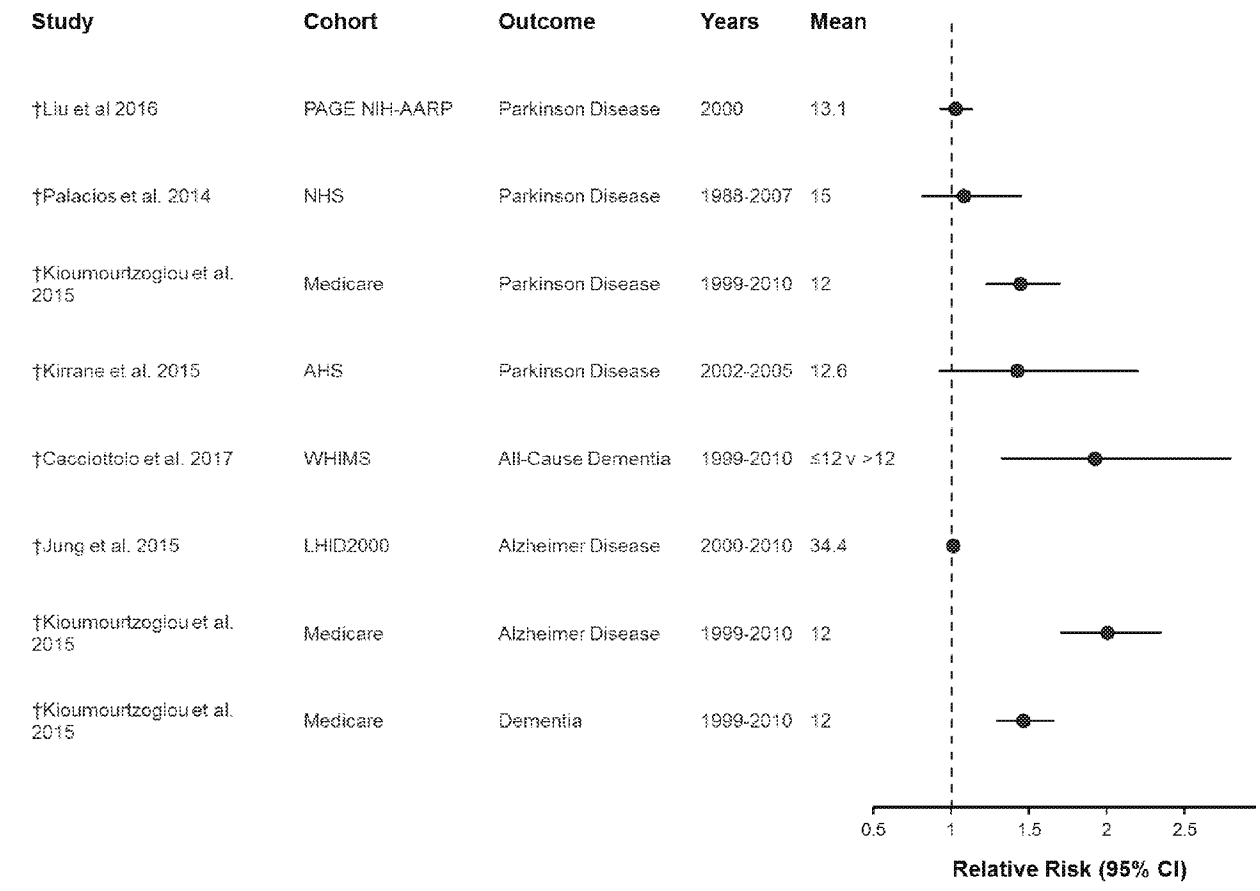
8.2.6 Neurodegenerative Diseases

There were no epidemiologic studies of the effect of long-term exposure to $PM_{2.5}$ and neurodegenerative disease evaluated in the previous ISA (U.S. EPA, 2009). A limited number of studies of Parkinson disease, Alzheimer's disease, and dementia are currently available for review (Figure 8-6, Table 8-15). Animal toxicological evidence of neurodegenerative diseases following long-term $PM_{2.5}$ exposure includes the demonstration of Parkinson disease-like brain histopathology (Veronesi et al., 2005), which is discussed in the 2009 PM ISA and in Section 8.2.4, and the demonstration of early markers of Alzheimer's disease (Bhatt et al., 2015), which is discussed in Section 8.2.3.

The set of studies of Parkinson disease includes a case control analysis from the Parkinson Genes and Environment study, National Institutes of Health, American Association of Retired People (PAGE NIH-AARP) study (Liu et al., 2016) and a prospective analysis from the NHS (Palacios et al., 2014). These studies are well-conducted in that self-reported outcomes were validated and individual-level data on an array of covariates including sex, smoking, and caffeine use was considered in the analyses. Although slightly increased, the relative risks reported in both studies were small relative to their wide confidence intervals, providing little evidence of an association [HR: 1.03 (95% CI 0.92, 1.13) in the PAGE NIH-AARP study and HR: 1.08 (95% CI: 0.81, 1.45) in the NHS study]. Kioumourtzoglou et al. (2015) reported large positive associations between long-term exposure to $PM_{2.5}$ and first hospital admission for Parkinson disease (ascertained using primary or secondary diagnosis code) indicating higher risk of Parkinson-related complications that require hospitalization among older adults receiving Medicare benefits in 50 Northeastern U.S. cities [HR: 1.44 (95% CI 1.22, 1.70)]. Although age and sex were controlled in the analysis, individual level data on smoking or dietary covariates was not available, nor was the outcome validated in this study. The other study of $PM_{2.5}$ exposure and Parkinson disease analyzed data from rural populations in North Carolina and Iowa reporting an imprecise, positive association between 4-year average $PM_{2.5}$ concentration and Parkinson disease (OR 1.34 95% CI: 0.93, 1.93) among farmers in North Carolina while no association was observed in among farmers in Iowa where exposures were much lower [OR: 0.91 (95% CI: 0.75, 1.11) per IQR (0.7 $\mu g/m^3$) increase] (Kirrane et al., 2015). Self-reported doctor-diagnosed Parkinson disease was validated for a subset of participants in this study.

Studies of Alzheimer's disease and dementia are also plotted on Figure 8-6. Some studies report positive associations with long-term $PM_{2.5}$ exposure, but findings are not consistent overall. In the analysis of the WHIMS cohort described previously, Cacciottolo et al. (2017) found an increased risk of all-cause dementia comparing 3-year moving average exposure to $PM_{2.5}$ of <12 $\mu g/m^3$ to ≥ 12 $\mu g/m^3$ [HR: 1.92 (95%CI: 1.32, 2.8)]. In a study in China where concentrations are relatively high, Jung et al. (2014) found little evidence of an association between annual average $PM_{2.5}$ exposure at baseline and Alzheimer's disease, although an increase in $PM_{2.5}$ during follow-up was associated with the disease. Similar to their

results for Parkinson disease Kioumourtzoglou et al. (2015) reported large associations of hospital admissions for Alzheimer's disease and dementia with $PM_{2.5}$ among Medicare recipients [HR: 2.0 (95%CI: 1.7, 2.35) and HR: 1.46 (95%CI: 1.29, 1.66), respectively].



Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in $\mu g/m^3$. Hazard Ratios are standardized to a 5 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table S8-4 (U.S. EPA, 2018).

AHS = Agricultural Health Study; LHID2000 = Longitudinal Health Insurance Database for 2000; NHS = Nurses Health Study, PAGE NIH-AARP = Parkinson's Genes and Environment study, National Institutes of Health-American Association of Retired People, WHIMS = Women's Health Initiative Memory Study.

†Studies published since the 2009 PM ISA.

Figure 8-6 Associations between long-term exposure to $PM_{2.5}$ and neurodegenerative diseases. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration unless otherwise noted.

Table 8-15 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and neurodegenerative diseases.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†Liu et al. (2016) 6 States, U.S. Case-control $PM_{2.5}$: 2000 Outcome: 1995–2006	PAGE NIH-AARP N = 1,556 cases N = 3,313 controls	Annual avg 1990 and 2000, kriging interpolation at residence, C-V R2 = 0.88	Range: 4.4–26.9 IQR 3.8	Neurologist confirmed PD in validation study (88% of cases)	Correlations (r): NO_2 r = 0.62 Copollutant model: NR
†Palacios et al. (2014) Longitudinal cohort $PM_{2.5}$: 1988–2007 (estimated from PM_{10} ratio prior to 1999) Outcome: 1990–2008	NHS N = 115,767 N = 508 PD cases	Cumulative avg up to 2 yr prior to PD onset, estimated spatiotemporal model at residential address [see (Puett et al., 2008)]	NR	Neurologist confirmed or medical record review PD	Correlations (r): PM_{10} r = 0.73; $PM_{10-2.5}$ r = 0.26 Copollutant model: NR
†Kioumourtzoglou et al. (2015) 50 cities, Northeastern US Longitudinal cohort $PM_{2.5}$: 1999–2010 Outcome: 1999–2010	Medicare 65+ yr N = 119,425 PD admissions N = 266,735 AD admissions N = 203,463 dementia admissions	City-specific avg assigned for each year of follow-up (1999–2010), adjusted for calendar year	12 (SD 1.6) IQR: 3.8	PD: ICD9 332 AD: ICD9 331 Dementia: ICD9 290	Correlations (r): NR Copollutant models: NR
†Kirrane et al. (2015) Case-control $PM_{2.5}$: 2002–2005 Outcome: 1993–2010	AHS farmers and spouses N = 301 cases N = 83,042 controls	4 yr avg, monitor plus CMAQ, 12 × 12 grid at residential address	NC: 12.6 IQR: 4.2 Iowa: 8.9 IQR 0.5	Self-reported doctor diagnosed Parkinson disease	Correlations (r): NR Copollutant models: NR
†Cacciottolo et al. (2017) Prospective cohort $PM_{2.5}$: 1999–2010 Outcome: 1995/99–2010	WHIMS n = 3,467 women (65–79 yr) w/specific APOE alleles	3 yr moving avg for geocoded residential history, BME-based spatiotemporal model, C-V R2 = 0.7	Median: 12.24 IQR: 10.67–14.16	Dementia (determined by central adjudication)	Correlations (r): NR Copollutant models: NR

Table 8-15 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and neurodegenerative diseases.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†Jung et al. (2014) Taiwan Longitudinal Cohort $PM_{2.5}$: 2000–2010 Outcome: 2001–2010	LHID2000 N = 95,960	Annual avg at baseline, IDW of 3 monitors within 25 km of postal code centroid for residence (also computed change in $PM_{2.5}$ from follow-up)	Mean (IQR) 34.4 (13)	ICD9 331 (consensus diagnosis in administrative database)	Correlations (r): Ozone r = 0.4, SO_2 r = 0.51 Copollutant model: NR

AD = Alzheimer's disease; AHS = Agricultural Health Study; BMI = Body Mass Index; BVAIT = B-Vitamin Atherosclerosis, Intervention Trial; CMAQ = Community Multiscale Air Quality; ELITE = Early versus Late Intervention Trial with Estradiol; LHID2000 = Longitudinal Health Insurance Database for 2000, NHS = Nurses' Health Study; PAGE NIH-AARP = Parkinson's Genes and Environment study, National Institutes of Health, American Association of Retired People; PD = Parkinson Disease; RCT = Randomized Clinical Trial; REGARDS = Reasons for Geographic and Racial Differences in Stroke; SALIA = Study of the Influence of Air Pollution on Lung Function, Inflammation, and Aging; WISH = Women's Isoflavone Soy Health.

†Studies published since the 2009 PM ISA.

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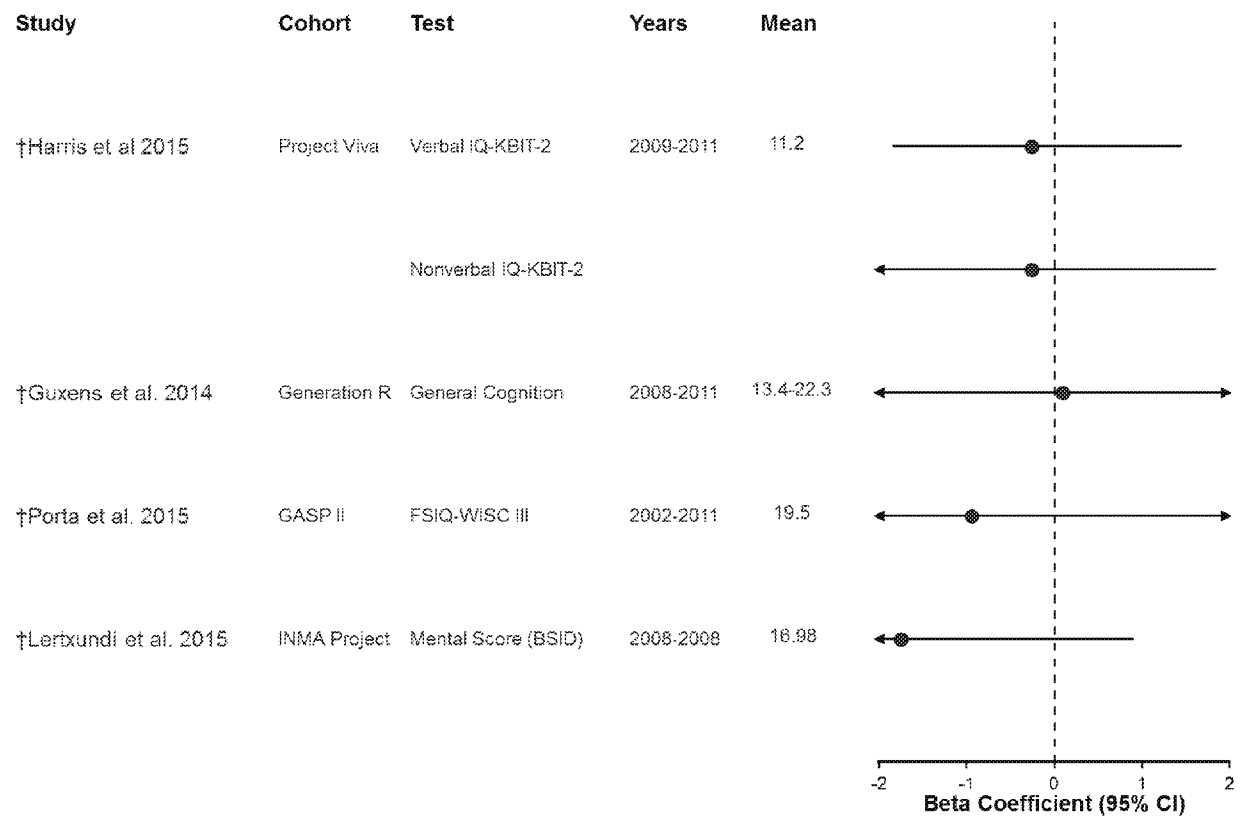
8.2.7 Neurodevelopmental Effects

There were no epidemiologic studies of neurodevelopmental effects in children available for review in the 2009 PM ISA. Currently there is a small body of literature examining the association of exposure to $PM_{2.5}$ during perinatal and childhood lifestages with cognitive and behavioral effects that do not provide consistent evidence of an association (Figure 8-7, Table 8-16). In addition, there is a limited number of studies examining the association of $PM_{2.5}$ during these lifestages with autism spectrum disorder (ASD). This set of studies report positive associations that are coherent with findings from an experimental animal study of $PM_{2.5}$ CAPs exposure demonstrating neuroinflammation and morphologic change that is associated with various human neuropathologies, including ASD.

8.2.7.1 Cognitive and Behavioral Effects

Harris et al. (2015) examined the effect of long-term $PM_{2.5}$ exposure during pregnancy and from birth through 6 years of age on cognition in children enrolled in Project Viva, which follows mother-infant pairs (N = 1,109) from birth through various lifestages during childhood. The weakly positive and negative associations with cognitive assessment scores that were reported did not provide evidence for an effect of $PM_{2.5}$ on cognition in these children. Porta et al. (2015) followed a cohort of infants born (n = 719) in Rome between 2003 to 2004 and administered the Wechsler Intelligence Scale for Children (WISC) III at age seven (n = 474). Authors reported associations with Full Scale [−0.95 (95% CI: −3.95, 2.05)], Verbal [0.22 (95% CI: −2.75, 3.20)] and Performance IQ [−2.05 (95% CI: −1.70, 0.60)], as well as results for several WISC subscales that provided little support for an association between pregnancy or childhood $PM_{2.5}$ exposures and cognitive effects. Guxens et al. (2014) reported no decrease in general cognition score in association with $PM_{2.5}$ exposure [β = 0.09 (95% CI: −2.95, 3.12)], although a decrease in psychomotor development was observed [β = −1.64 (95% CI: −3.47, 0.18)]. Lertxundi et al. (2015) reported decrements in motor scale score with increasing $PM_{2.5}$ concentrations but little evidence of an association with mental score on the Bayle Scale of Infant Development (BSID). Results persisted after adjustment for NO_2, and associations were relatively large closer to roads and pollution producing facilities. $PM_{2.5}$ exposures was associated with decreases on tests of attention (continuous performance and stroop) but not with other neurobehavioral tests in the COGNAC study (Saenen et al., 2016).



Circles represent beta coefficients; horizontal lines represent 95% confidence intervals. Red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Concentrations are in $\mu g/m^3$. Results are standardized to a 5 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table S8-5 (U.S. EPA, 2018).

BSID = Bayley Scale of Infant Development, FSIQ = Full Scale Intelligence Quotient, GASP = Gene and Environment Prospective Study on Infancy, INMA = Childhood and the Environment Cohort, KBIT−2 = Kaufman Brief Intelligence Test Second Edition, WISC = Wechsler Intelligence Scale for Children.

†Studies published since the 2009 PM ISA.

Figure 8-7 Associations between long-term exposure to $PM_{2.5}$ and cognitive effects. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration (unless otherwise noted).

Table 8-16 Studies of the association between short-term $PM_{2.5}$ exposure and cognitive effects in children.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Harris et al. (2015) Eastern Massachusetts $PM_{2.5}$: 2009–2011 Outcome: 1999/02–2011	Project Viva Children (mean = 8 yr) N = 1,109	6 yr avg, LUR with satellite derived AOD	Mean: 11.3 (SD: 1.7)	Verbal IQ Non-verbal IQ Visual motor Design memory Picture memory	Correlations (r): NR Copollutant models: NR
†Guxens et al. (2014) 6 European Cohorts $PM_{2.5}$: 2008–2011 Outcome: 1997–2008	Generation R N = 9,482 Children 1–6 yr	LUR to estimate concentration at residence of birth, back extrapolated through pregnancy	Mean Range: 13.4–22.3	General cognition, language development, global psychomotor development at 1–6 yr of age (test depended on cohort):	Correlations (r): NR Copollutant models: NR
†Porta et al. (2015) Rome, Italy Prospective Cohort $PM_{2.5}$: 2010–2011 Outcome: 2002–2011	GASPII Children 7 yr N = 474	Pregnancy avg and avg from birth to age 7, LUR fit using 40 monitors, assigned at residence, C-V R2 = 0.79	Mean 19.5 (SD: 2.2) IQR 2	WISC III (13 subtests)	Correlations (r): NR Copollutant models: NR
†Lertxundi et al. (2015) Guipuzcoa valleys, Spain 2006–2008	INMA N = 438	Trimester avg of nearest monitor (van Buuren, 2007)	16.98 (SD: 6.57)	BSID at 13–18 mo	Correlations (r): r = 0.045 NO_2 Copollutant correlations: NR

Table 8-16 (Continued): Studies of the association between short-term $PM_{2.5}$ exposure and cognitive effects in children.

Study Location/Years	Study Population	Exposure Assessment	Concentration $\mu g/m^3$	Outcome	Copollutant Examination
†Saenen et al. (2016) Flanders, Belgium $PM_{2.5}$: 2011–2013	COGNAC Children	Daily avg, spatiotemporal model (satellite, land cover and monitor data), at school and at residential address, lags 0–2 days R2 = 0.8	Median 15.7 IQR 1.16 at home	Attention: continuous performance, Stroop Memory: digit span forward, digit span backward Visual processing speed: digit symbol, pattern comparison	Correlations (r): NR Copollutant models: NR

BC = Black Carbon; BSID = Bayley Scale of Infant Development; COGNAC = Cognition and Air Pollution in Children study; GASP = Gene and Environment Prospective Study on Infancy; INMA = Childhood and the Environment Cohort; NR = Not Reported; WISC = Wechsler Intelligence Scale for Children.

†Studies published since the 2009 PM ISA.

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8.2.7.2 Autism

Autism is a condition that includes a spectrum of impairments affecting social interaction, language development, and communication skills that often involves rigid and repetitive behaviors.

Epidemiologic Studies

At present, there is a European pooled cohort study that examined autistic traits and multiple U.S.-based case-control studies that examine ASD in association with $PM_{2.5}$ exposure during pregnancy. Guxens et al. (2015) observed no associations between $PM_{2.5}$ during pregnancy and either borderline clinical or clinical autistic traits using information from cohort studies across four European countries. Of the case-control studies examining ASD, two used monitors to assign $PM_{2.5}$ exposures (Becerra et al., 2013; Volk et al., 2013), while the others used LUR methods to assign exposure (Raz et al., 2015; Talbott et al., 2015). Positive associations were observed between $PM_{2.5}$ exposures and ASD in studies that used both monitors and LUR models to assign exposure and for various exposure periods used in different studies. Volk et al. (2013), Talbott et al. (2015), and Raz et al. (2015) observed positive associations similar in magnitude for both entire pregnancy exposure and first year of life exposure. Specifically, Volk et al. (2013) observed positive associations for both entire pregnancy exposure (OR range: 1.52, 95% CI: 1.46, 1.59) and first year of life exposure (OR: 1.54, 95% CI: 1.24, 1.92) in a California population. In a six-county region of southwestern Pennsylvania, Talbott et al. (2015) observed positive associations with $PM_{2.5}$ exposure during pregnancy (OR: 1.38, 95% CI: 0.80, 2.36]) and first year of life (OR: 1.74, 95% CI: 0.91, 3.30), as well as cumulative exposures from three months pre-conception through first year of life (OR: 1.97, 95% CI: 0.97, 4.04). Raz et al. (2015) reported a positive OR for ASD with entire pregnancy exposure, after adjusting for exposures nine months before and after pregnancy (OR: 1.74, 95% CI: 1.08, 2.47). In Los Angeles, Becerra et al. (2013) reported a positive OR for ASD with entire pregnancy exposure (OR: 1.07, 95% CI: 1.00, 1.16), though the magnitude was lower than that observed in the other studies. Building on the positive associations observed by Volk et al. (2013), follow-up studies provide some initial evidence for gene-environment interactions with $PM_{2.5}$ concentrations and MET receptor variants (Volk et al., 2014) but not for copy number variation (Kim et al., 2017). Interpretation of these results is limited by the lack of control for potential confounding by copollutants, the small number of studies, and uncertainty regarding critical exposure windows (Table 8-17).

Table 8-17 Studies of the association of long-term exposure to $PM_{2.5}$ and Autism Spectrum Disorders.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Guxens et al. (2015) Cross-sectional $PM_{2.5}$: 2008–2011 with back extrapolation	ESCAPE Mother child pairs, n = 8,079	LUR to estimate $PM_{2.5}$ at birth residence (pregnancy period)	NR	Autistic traits using A-TAC	Correlations (r): NR Copollutant models: NR
†Volk et al. (2013) Population based case-control California (state-wide) 1997-2008	CHARGE n = 279 cases, n = 245 controls 24–60 mo old	IDW of 4 closest monitors within 50 km	NR	Evaluation in person using ADOS and parent administered ADI-R	Correlations (r): PM_{10} r = 0.84, Ozone r = 0.26, NO_2 = 0.64 Copollutant models: NR
†Becerra et al. (2013) Case control Los Angeles, CA Births: 1995-2006 AD diagnosis: 1998-2009	N = 7,603 cases (10 controls per case) 3–5 yr	Nearest ambient monitor and LUR, concentration during pregnancy linked to residence at birth	Mean: 19.6	Primary diagnosis of AD (DSM IV-R)	Correlations (r): CO r = 0.6, NO r = 0.58, Ozone r = −0.47, PM_{10} r = 0.58 Copollutant models: NR
†Raz et al. (2015) Nested case control 50 states, US	NHS n = 245 cases, n = 1,522 controls	Spatiotemporal model (Yanosky et al., 2009) to estimate exposure at residence before, during and after pregnancy.	NR	Self-report on telephone interview to ascertain autistic disorder using parent administered ADI-R; SRS for 90% of eligible cases	Correlations (r): NR Copollutant models: NR

Table 8-17 (Continued): Studies of the association of long-term exposure to $PM_{2.5}$ and Autism Spectrum Disorders.

Study Location/Years	Study Population	Exposure Assessment	Concentration $\mu g/m^3$	Outcome	Copollutant Examination
†Talbott et al. (2015) Case-control S.W. Pennsylvania 2005–2009	Mother, infant pairs, n = 217 cases and 226 controls	LUR to estimate exposure at residence 3 mo prior and 2 yr after birth	14.1 (pre-pregnancy through age 2)	Score ≥15 on SCQ, documentation including ADOS or diagnosis from psychologist	Correlations (r): NR Copollutant models: NR

AD = Autism Disorder, ADI-R = Autism Diagnostic Interview-Revised, A-TAC = Autism—Tics, Attention Deficit and Hyperactivity Disorders, and Other Comorbidities, ADOS = Autism Diagnostic Observation Schedule, CHARGE=Childhood autism risks from Genetics and the Environment Study, DSM IV-R, Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision, ESCAPE = European Study of Cohorts for Air Pollution Effects, IDW = inverse distance weighting, LUR = land use regression, N, n = number of subjects, NHS II = Nurses' Health Study II, NR = not reported, SCQ = Social Communication Questionnaire, SRS = Social Responsiveness Scale.

†Studies published since the 2009 PM ISA.

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Animal Toxicological Studies

Klocke et al. (2017) examined the effects of prenatal exposure (GD0.5 to GD16.5) to $PM_{2.5}$ CAPs in Sterling Forest, NY using B6C3F1 mice (Table 8-18). At postnatal day (PND) 11−15, both male and female offspring had increased microglial activation, an indicator of inflammation, in the corpus callosum ($p < 0.05$). Males had decreased total number of microglia ($p < 0.05$) and females trended in this direction (not significant) but had increased iron deposition in the corpus callosum ($p < 0.05$). In the hippocampus, female offspring had increases in activated microglia ($p < 0.01$) with no change in number of microglia; the male hippocampal microglia were not affected. In addition, both male and female offspring had ventriculomegaly, increased corpus callosum area and hypermyelination, and reduced hippocampal area ($p < 0.05$). Frontal cortex thickness was not affected by CAPs exposure. Various human neuropathologies are associated with ventriculomegaly including schizophrenia, ASD, and ADHD.

Table 8-18 Study-specific details from an animal toxicological study of long-term exposure and neurodevelopmental effects.

Study	Study Population	Exposure Details	Endpoints Examined
Klocke et al. (2017)	Male and female B6C3F1 mice (8−10 weeks old) were mated and then dams were exposed to Sterling Forest, NY CAPs.	Prenatal exposure to filtered air or Sterling Forest $PM_{2.5}$ CAPs for 6h/day during gestation (GD0.5 to GD 16.5). Mean CAPs concentration over the exposure period averaged 92.7 ± 19.2 (mean ± SD) $\mu g/m^3$ compared to 3.5 ± 0.9 $\mu g/m^3$ for FA controls. CAPs exposure levels ranged from 32.95 to 184.43 $\mu g/m^3$ over the duration of the exposure period. PM was a mixture of $PM_{2.5}$ and UFP	Offspring neuropathological outcomes including brain structure and size (ventriculomegaly), microglial activation (inflammation), myelination, corpus callosum iron content in association with myelination.

CAPs = concentrated ambient particles; FA = filtered air; GD = gestational day.

8.2.8 Components and Sources of $PM_{2.5}$

No studies relevant to our understanding of the effect of long-term exposure to components or sources of $PM_{2.5}$ were evaluated in the 2009 PM ISA (U.S. EPA, 2009). Currently, there are several studies of traffic exposures among children as well as a study of adults available for consideration (Table 8-18Table 8-18). These studies examine cognitive effects in the populations studied. Overall, the evidence

base remains limited and the few available studies do not provide evidence to support an independent effect of sources or components of $PM_{2.5}$ that is distinct from the effect long-term exposure to $PM_{2.5}$ mass.

Basagaña et al. (2016) conducted an analysis of the data previously examined by Sunyer et al. (2015) and described in Section 8.6.6. In this longitudinal repeated measures study, the authors report lower growth in memory and attentiveness in association with metrics for traffic-related $PM_{2.5}$ derived using constrained positive matrix factorization (PMF) based on 33 chemical species. Chen et al. (2016) conducted a repeated measures analysis of the association of long-term $PM_{2.5}$ and BC exposure with measures of attention, memory and processing in children. Long-term exposure to $PM_{2.5}$ was associated with decreased performance on measure of attention, while little evidence of associations with BC was provided by the study. Finally, the cross-sectional analysis of Project Viva participants reported by Harris et al. (2015) did not show an association between BC and cognitive effects. Among adults, Tonne et al. (2014) used a set of tests designed to measure reasoning, memory, semantic fluency, and phonemic fluency to examine the association with long-term exposure to $PM_{2.5}$ from traffic, estimated using a dispersion model. $PM_{2.5}$ from traffic was exhibited a similar pattern of association with cognition as with $PM_{2.5}$ mass.

Table 8-19 Characteristics of the studies examining the association between long-term exposure to $PM_{2.5}$ sources and components and cognitive function.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Harris et al. (2015) Eastern Massachusetts BC: 2009–2011 Outcome: 1999/02–2011	Project Viva Children (mean = 8 yr) N = 1,109	6 yr avg, LUR with satellite derived AOD	Mean: 0.56 (SD: 0.16)	Verbal IQ Non-verbal IQ Visual motor Design memory Picture memory	Correlations (r): NR Copollutant models: NR
†Basagaña et al. (2016) Barcelona, Spain Jan 2012-Mar 2013	N = 2,618 School Children, Barcelona	Source specific $PM_{2.5}$ using source apportionment assigned to the school: mineral, traffic, organic/textile/chalk, secondary sulfate and organics, secondary nitrate, road dust, metallurgy, sea spray, heavy oil combustion	Median $PM_{2.5}$ outdoors 28 Median $PM_{2.5}$ indoors 36	Working memory Superior working memory Inattentiveness	Correlations (r): NR Copollutant models: NR
†Saenen et al. (2016) Flanders, Belgium 2011-2013	COGNAC Children	Annual avg BC prior to testing, spatiotemporal model (satellite, land cover and monitor data) C-V R2 = 0.8	Median 1.54 IQR 0.20	Stroop (selective attention), Continuous performance (sustained attention), Digit Span Forward and Backward (short-term memory), Digit Symbol and Pattern Comparison (visual processing)	Correlations (r): NR Copollutant models: NR

Table 8-19 (Continued): Characteristics of the studies examining the association between long-term exposure to $PM_{2.5}$ sources and components and cognitive function.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Tonne et al. (2014) Greater London Longitudinal Cohort $PM_{2.5}$ (exhaust) 2003–2009 Outcome: 2007/2009	Whitehall II (mean 66 yr) N = 2,867	1 yr avg, 1 yr lag 4, 3 yr avg, 5 yr avg, dispersion model, r = 0.74 (2008, 15 monitors)	5 yr avg 0.64 IQR: 1.1	Cognitive test performance 5 yr decline	Correlations (r): NR Copollutant models: NR

AOD = Aerosol Optical Depth, BC = Black Carbon; COGNAC = Cognition and Air Pollution in Children study; C-V = Cross-Validation; IQR = Inter-quartile Range; LUR = Land Use Regression; NR = Not Reported; TRAP = Traffic Related Air Pollution.

†Studies published since the 2009 PM ISA.

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8.2.9 Summary and Causality Determination

The evidence that long-term exposure to $PM_{2.5}$ can affect the nervous system has grown substantially since the 2009 PM ISA (U.S. EPA, 2009). There is evidence from animal toxicological studies demonstrating a link between long-term $PM_{2.5}$ exposure-mediated activation of the SNS and downstream cardiovascular effects. In addition, evidence for neuroinflammation and downstream consequences is well substantiated and coherent across experimental animal and epidemiologic studies. Specifically, toxicological studies in adult animals demonstrate neuroinflammation, neurodegeneration, indicators of Alzheimer's disease, impaired learning and memory, and altered behavior. High quality epidemiologic studies provide support, reporting changes in brain morphology (i.e., neurodegeneration), cognitive decrements and dementia in adult populations. The evidence characterizing the relationship between long-term exposure to $PM_{2.5}$ and effects on the nervous system is detailed below (Table 8-20), using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015).

Animal toxicological studies of long-term $PM_{2.5}$ exposure provide evidence that the central nervous system mediates responses outside of the brain, i.e., peripheral responses. One study linked hypertension to an increase in sympathetic tone (Ying et al., 2014). Another study in a mouse model of diabetes linked exaggeration of the diabetic phenotype to hypothalamic inflammation (Liu et al., 2014). A relationship between hypothalamic inflammation and sympathetic tone was proposed (Ying et al., 2014).

Long-term exposure of adult animals resulted in inflammation and neurodegeneration in specific regions of the brain including the hippocampus (Fonken et al., 2011). Changes in the hippocampus were accompanied by impaired learning and memory and by altered behavior (Fonken et al., 2011). Long-term exposure to $PM_{2.5}$ was associated with accelerated global cognitive decline in longitudinal analysis of women enrolled in WHIMS (Cacciottolo et al., 2017). This decline was larger among those with APOE alleles thought to confer an increased risk of Alzheimer's disease. Further, morphologic changes (i.e., reduction in total WM, subcortical WM and cortical GM) compatible with these observations of cognitive decline were also observed in this cohort (Casanova et al., 2016; Chen et al., 2015). In a cross-sectional analysis of the Framingham Heart Offspring study Wilker et al. (2015) reported that total cerebral brain volume was smaller with increasing $PM_{2.5}$. Decrements on cognitive tests were observed in longitudinal analyses of the NHS and in the British Whitehall II cohort (Tonne et al., 2014; Weuve et al., 2012). Wilker et al. (2015) and Weuve et al. (2012) are notable in that they controlled for a wide range of covariates including SES and vascular factors. None of these studies considered copollutant confounding, however. Cross-sectional analyses were less consistent in their observation of associations between long-term $PM_{2.5}$ exposure and cognitive function. Specifically, cognitive impairment was not associated with long-term $PM_{2.5}$ exposure in the REGARDS (Loop et al., 2013) or SALIA cohorts (Schikowski et al., 2015) while positive associations were reported in U.S. surveys (Tzivian et al., 2016; Ailshire and

Crimmins, 2014) and in an analysis of clinical trial participants from southern California (Gatto et al., 2014).

Evidence for a relationship between long-term $PM_{2.5}$ exposure and Alzheimer's disease and dementia is provided by both animal toxicological and epidemiologic studies. Early markers of Alzheimer's disease pathology were increased in the temporal cortex of mice exposed to $PM_{2.5}$ CAPs for 9 months, but not 3 months (Bhatt et al., 2015). An association between long-term $PM_{2.5}$ exposure and all-cause dementia was observed among WHIMS participants (Cacciottolo et al., 2017) and with hospitalizations among Medicare recipients for Alzheimer's disease and dementia, which may be related to complications from the disease (Kioumourtzoglou et al., 2015). However, a large registry-based study conducted in China, where exposure levels are high relative to the U.S., reported no evidence of an association with Alzheimer's disease (Jung et al., 2014).

Although an experimental animal study demonstrating loss of dopaminergic neurons in the substantia nigra (Veronesi et al., 2005) provides biological plausibility for an association of long-term $PM_{2.5}$ exposure with Parkinson disease, associations were not consistently observed in epidemiologic studies. Incident case control or longitudinal analyses relying on neurologist confirmed Parkinson disease, provided no evidence of an association with $PM_{2.5}$ (Liu et al., 2016; Palacios et al., 2014). There was some evidence that long-term exposure to $PM_{2.5}$ was associated with hospital admission for Parkinson disease in the aforementioned study of Medicare recipients indicating the potential for long-term exposure to $PM_{2.5}$ to increase the risk of complications that require hospitalization in neurodegenerative disease patients (Kioumourtzoglou et al., 2015).

Several studies of the association of $PM_{2.5}$ exposure during pregnancy or other childhood lifestage with cognitive or motor development in children were conducted. Studies have generally found little evidence of association with cognitive development for entire pregnancy, third trimester or childhood exposures (Harris et al., 2015; Lertxundi et al., 2015; Porta et al., 2015; Guxens et al., 2014). Where decrements on tests of cognition were observed, confidence intervals were wide. Associations with ASD were observed in several epidemiologic studies but the interpretation of these findings was limited by the lack of control for potential confounding by copollutants, the small number of studies, and uncertainty regarding critical exposure windows. Biological plausibility for associations observed of $PM_{2.5}$ with ASD is provided by an animal toxicological study. Klocke et al. (2017) reported inflammatory and morphologic changes in corpus callosum and hippocampus, as well as ventriculomegaly in young animals exposed prenatally to $PM_{2.5}$ CAPs.

The strongest evidence of an effect of long-term exposure to $PM_{2.5}$ on the nervous system is provided by animal toxicological studies that show inflammation, oxidative stress, morphologic changes, and neurodegeneration in multiple brain regions following long-term exposure to $PM_{2.5}$ CAPs. These findings are coherent with a number of epidemiologic studies report consistent associations with cognitive decrements and with all cause dementia. **Overall, the collective evidence is sufficient to conclude that a causal relationship is likely to exist between long-term $PM_{2.5}$ exposure and nervous system effects.**

Table 8-20 Summary of evidence for a likely to be causal relationship between long-term $PM_{2.5}$ exposure and nervous system effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Brain Inflammation and Oxidative Stress			
Consistent evidence from multiple toxicological studies at relevant $PM_{2.5}$ concentrations	Multiple toxicological studies in adult animals demonstrate changes in the hippocampus	†Fonken et al. (2011) †Hogan et al. (2015) †Tyler et al. (2016)	94.4 µg/m^3 94.4 µg/m^3 315.3 µg/m^3
	cerebral cortex	Campbell et al. (2005) †Bhatt et al. (2015)	441.7 µg/m^3 65.7 µg/m^3
	hypothalamus	†Ying et al. (2014) †Ying et al. (2015) †Liu et al. (2014) †Tyler et al. (2016)	107 µg/m^3 128.3 µg/m^3 107 µg/m^3 315.3 µg/m^3
	Inhibition of hypothalamic inflammation blocked metabolic effects.	†Liu et al. (2014)	107 µg/m^3
Activation of the Sympathetic Nervous System			
Limited toxicological evidence at relevant $PM_{2.5}$ concentrations	Inhibition of SNS resulted in decreased blood pressure	†(Ying et al., 2014)	107 µg/m^3
Reduced Cognitive Function and Neurodegeneration Adults			
High quality epidemiologic studies of established cohorts report reductions in brain volume	Evidence from WHIMS and Framingham Offspring report associations with reduced WM volume	†(Chen et al., 2015) †(Casanova et al., 2016) †(Wilker et al., 2015)	12.24 µg/m^3 NR 11.1 µg/m^3
Uncertainty regarding the independent effect of the PM2.5 association	Copollutant model results lacking		
Coherence provided by evidence from toxicological studies at relevant $PM_{2.5}$ concentrations	Toxicological studies demonstrate neurodegenerative changes in substantia nigra or hippocampus	†Veronesi et al. (2005) †Fonken et al. (2011) †(Hogan et al., 2015, pp. author-year)	110 µg/m^3 94.4 µg/m^3 94.4 µg/m^3

Table 8-20 (Continued): Summary of evidence for a likely to be causal relationship between long-term $PM_{2.5}$ exposure and nervous system effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
High quality epidemiologic studies of established cohorts report consistent associations with reduced cognitive function.	Longitudinal analyses of WHIMS, NHS and Whitehall II report associations with cognitive decline.	†Cacciottolo et al. (2017) †Weuve et al. (2012) †Tonne et al. (2014)	12.2 µg/m^3 8.5 µg/m^3 (5 yr avg) 14.9 µg/m^3
Coherence provided by toxicological studies of cognitive effects	Impaired learning and memory demonstrated in mice	†Fonken et al. (2011) †Hogan et al. (2015)	94.4 µg/m^3 94.4 µg/m^3
Inconsistent evidence from studies of neurodegenerative diseases	High quality studies relying on neurologist confirmed PD provided no evidence of an association. Association with all-cause dementia determined by physician adjudication observed in WHIMS but not in registry based follow-up study of Alzheimer's disease in China.	†Liu et al. (2016) †Palacios et al. (2014) †Cacciottolo et al. (2017) †Jung et al. (2014)	4.4–26.9 µg/m^3 NR 12.2 µg/m^3 34.4 µg/m^3
Neurodevelopmental Effects in Children			
Evidence from limited number epidemiologic studies of autism generally positive, but with substantial uncertainties remaining	U.S. case-control studies observe positive associations with $PM_{2.5}$ exposures and ASD. European pooled cohort study observed no associations with clinical autistic traits.	Section 8.2.7.2	14.0–19.6 µg/m^3
Uncertainty regarding the independent effect of PM2.5 and the critical window of exposure	Copollutant model results are lacking and the critical expsoure window is not known		
Limited and inconsistent epidemiologic evidence for other neurodevelopmental outcomes	Generally null or inconsistent associations between $PM_{2.5}$ exposures and cognitive assessment scores	Section 8.2.7.1	

Table 8-20 (Continued): Summary of evidence for a likely to be causal relationship between long-term $PM_{2.5}$ exposure and nervous system effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Limited toxicological evidence providing coherence	Neuroinflammation and morphologic changes including ventriculomegaly were demonstrated following prenatal exposure	†Klocke et al. (2017)	92.7 μg/m^3
Biological Plausibility			
Biological plausibility provided by animal toxicological and epidemiologic studies	Pathways involving (1) SNS activation and (2) inflammation leading to morphologic changes in the brain, neurodegeneration and neurodevelopmental effects are demonstrated	Section 8.2.1	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is characterized.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated (for experimental studies, ≤2 mg/m^3).

†Studies published since the 2009 PM ISA.

8.3 Short-term $PM_{10-2.5}$ Exposure and Nervous System Effects

The previous ISA did not report any studies of nervous system effects as a result of short-term exposure to $PM_{10-2.5}$. Although the evidence continues to be limited, there are some recent studies available for review. The discussion opens with a discussion of biological plausibility (Section 8.1.1) that provides background for the subsequent sections in which groups of related endpoints are presented in the context of relevant disease pathways. These outcome groupings are activation of the SNS and HPA stress Axis (Section 8.1.2) and brain inflammation and oxidative stress (Section 8.1.3). The collective body of evidence is integrated[73] across and within scientific disciplines, and the rationale for the causality determination is outlined in Section 8.3.4.

[73] As detailed in the Preface, risk estimates are for a 10 μg/m3 increase in 24-hour avg PM10−2.5 concentrations unless otherwise noted.